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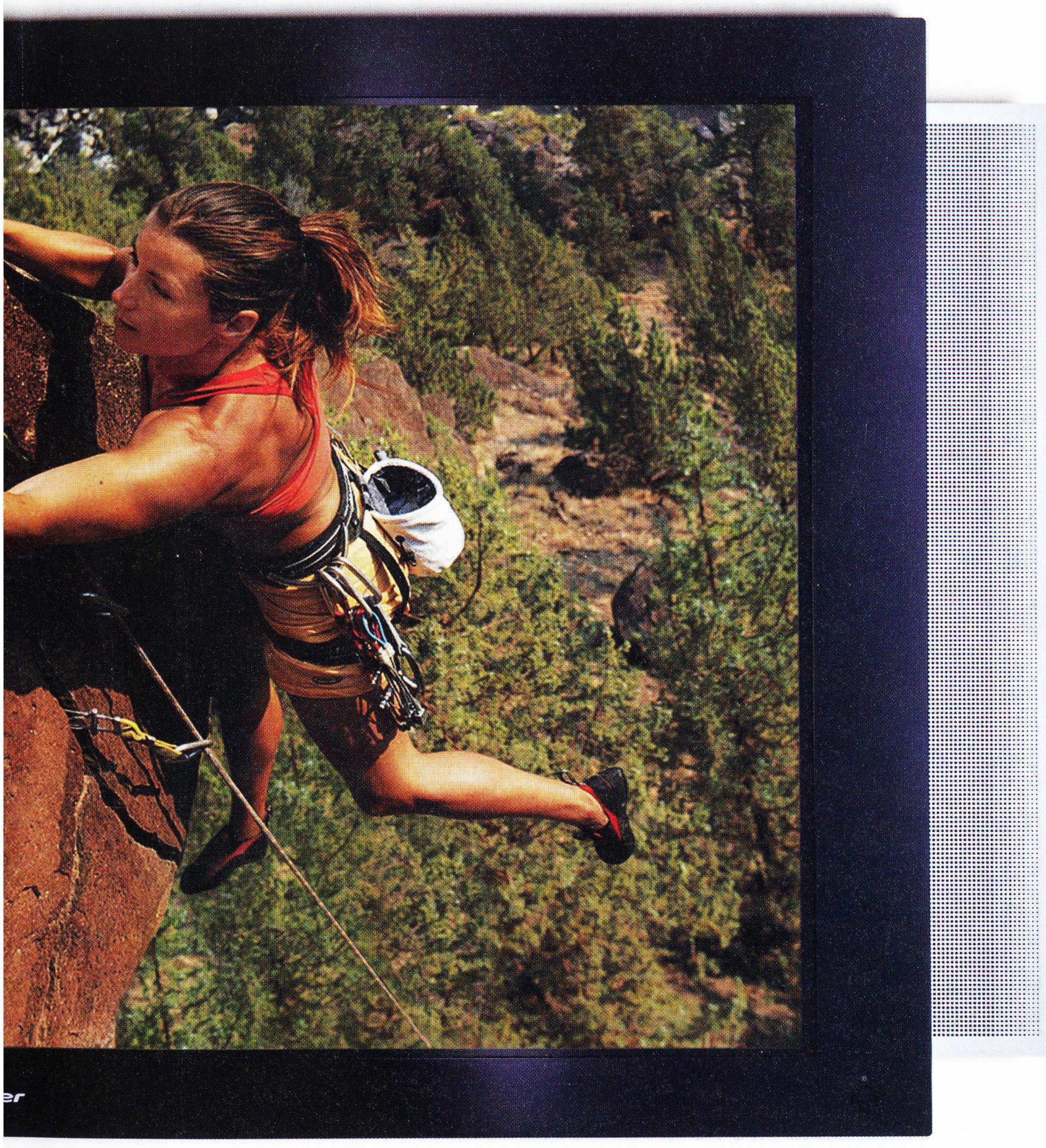

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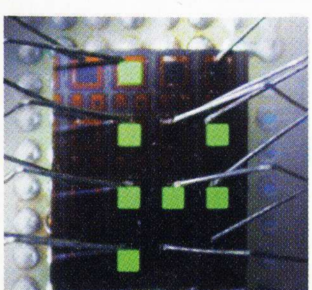
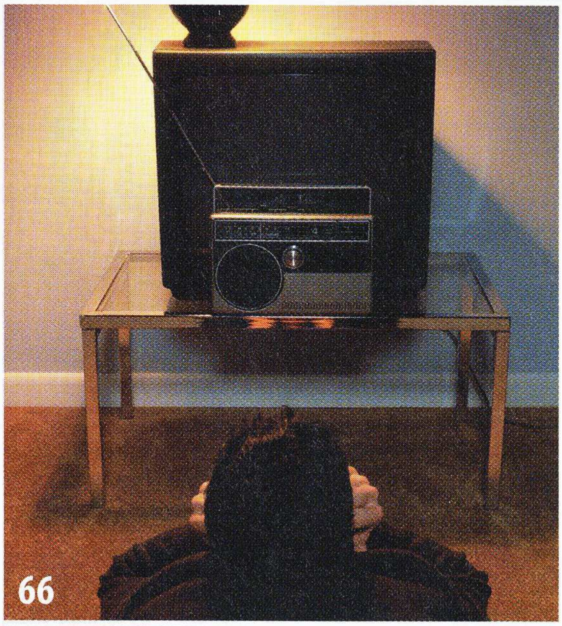


Technology Review
Volume 107, Number 1
February 2004

"All these technologies have been written off as road kill on the highway of progress." *p. 66*



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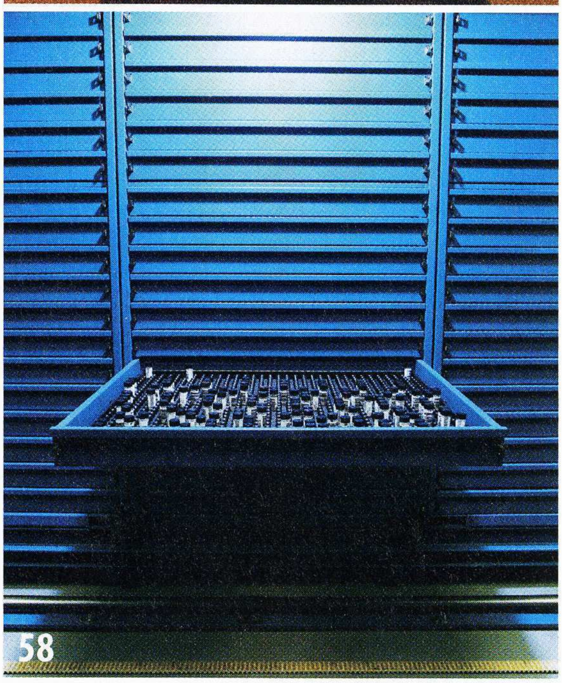

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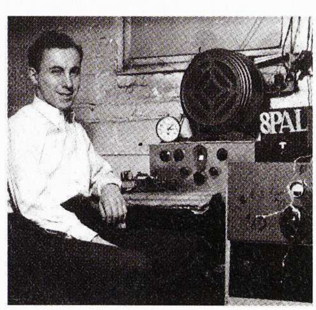

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HYBRID SYNERGY DRIVE

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Thinking about Thinking

CREATIVE THOUGHT IS THE LIFEBLOOD OF INNOvation. Only it's hard to think creatively in the middle of the daily grind. Individuals and companies have grappled with this conundrum for ages: IBM was famous for the "Think" signs that once permeated its offices. But the dilemma seems more pronounced than ever in today's era of e-mail, cell phones, and general 24/7 blur. When I do have time to think, I often think about how to think better.

In the mid-1980s, I reported a *Time* cover story on the idea that asteroids or comets hitting the earth had created a global dust storm that choked off sunlight and disrupted the food chain, ultimately causing the dinosaurs' extinction. The theory's chief originator was the late Nobel Prize–winning physicist Luis Alvarez. Alvarez was not just a great scientist but a National Inventors Hall of Fame inductee whose inventions included an aircraft blind-landing system, which saved many lives by providing pilots a radar-guided path in poor-visibility conditions, and a photographic lens that became standard in Polaroid cameras.

Alvarez's trademark was a unique ability to combine his imagination with the facts. In the dinosaurs' case, Alvarez's insights led to the discovery of a worldwide layer of the element iridium that formed at about the time of the beasts' extinction. Some theorized it came from volcanic eruptions, others a supernova. But Alvarez ruled these out, showing that a comet or asteroid was far more likely.

How did he get that way? Well, obviously, Alvarez had great natural gifts. But his father also played a role. A physician and medical researcher who missed out on his own Nobel Prize because he had not taken time to think carefully about his work and its progress, the elder Alvarez raised his son to devote a half-hour every day to pondering what he knew and what its implications might be.

Despite being at the forefront of technology, nobody cites technology as a tool for thinking better.

As we prepared to unveil our annual selection of "10 Emerging Technologies That Will Change Your World" *(p. 32)*, I asked some of the innovators profiled how they do their best thinking. But while I did get some intriguing responses that hold insights and reminders for us all, I found myself even more curious about the implications of what I got back.

John Rogers of the University of Illinois, who's developing microfluidic optical fibers, likes the "Open Road" strategy. Says Rogers, "I occasionally arrange to fly back in to Chicago rather than all the way to Champaign. The drive is about two hours—straight, flat driving. This provides a great opportunity to think without too many distractions." Don Arnone of TeraView, a leader in the hot field of t-rays, finds the same escape in his hour-long commute to and from his London offices. He calls it "an inadvertent bonus of the realities of modern life."

Both Rogers and Stanford University's Daphne Koller—an expert in probabilistic machine learning—cite the perspectives provided by students as spurs to creative thought. "Interactions with my graduate students, where we really brainstorm about a problem, are the most productive times that I have," Koller says. Rogers extols the benefits of having to relate his ideas to a diverse group. "Explaining concepts in many cases requires one to think about a problem in different ways, in order to find the most effective way of communicating a thought," he says.

These are important points, because poor communication is a huge barrier to creativity and the successful implementation of ideas. People often need to say the same things in different ways, depending on whom they are speaking with—and that change in mindset can spur other good ideas. When, as frequently happens, people don't bother searching for different ways to communicate an idea and instead expect their listeners or readers to just "get it," creativity is stifled.

Sometimes creativity can be orchestrated: designing open spaces to stimulate interaction is a hallmark of corporate and university labs. Many scoff at such attempts. But Christian Rehtanz, who is developing methods for real-time control of the power grid at ABB, finds them useful. "In the research center of ABB, we had the slogan 'coffee break patents,'" he says. The break room boasts comfortable chairs, a nice view, and some interactive games, like Lego blocks. "Frequently, people came together and started a not-very-serious discussion on crazy things to be patented," he says. "Most of that was not useful for ABB, but a lot of these ideas are doing now a good business."

Perhaps more telling is that despite being at the forefront of technology, nobody cites technology as a tool for thinking better. I'm going to think about that. **Robert Buderi**

A BRIGHTER *TR*

Beginning with this issue, *Technology Review* is being printed on UPM Satin paper. It's a whiter, brighter, slightly glossier stock than our previous Choctaw Matte, which we think enhances the new design unveiled in October. We hope it makes reading *TR* even more enjoyable.

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TECHNOLOGY REVIEW

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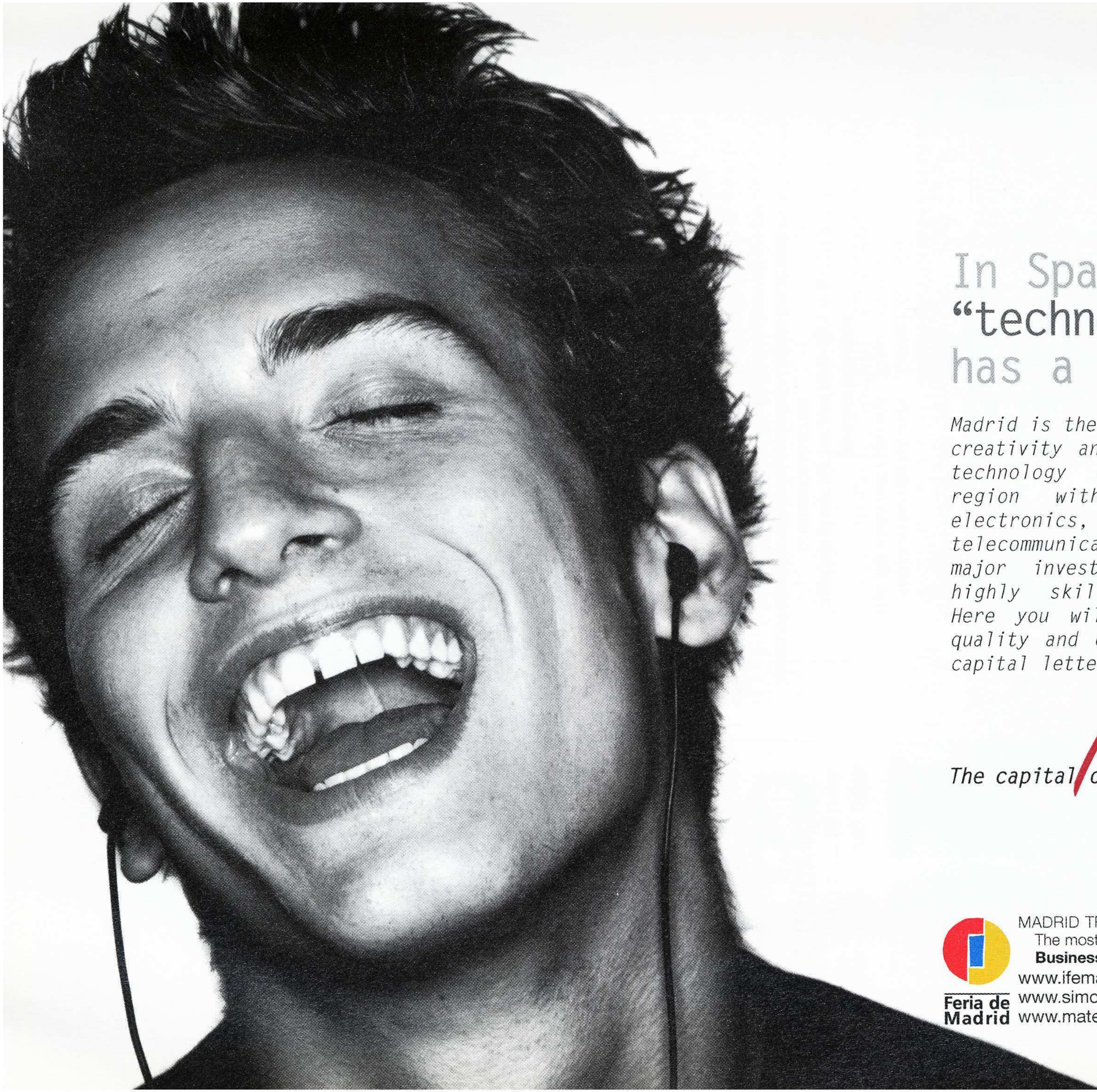

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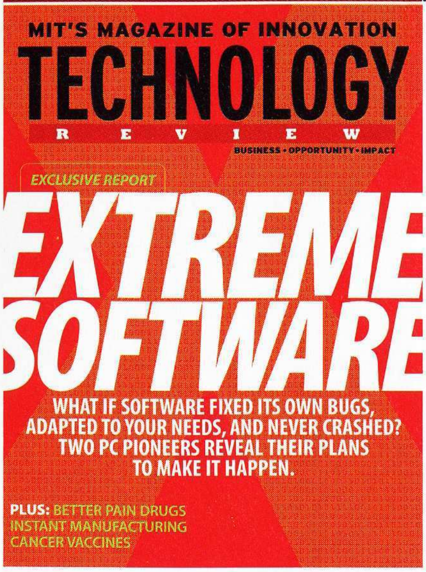

"[When] accountants and insurance specialists can write their own software, we will discover how bad software can get."

EXTREME SOFTWARE

I CANNOT AGREE WITH THE PREMISE that the problem with software is programmers ("Everyone's a Programmer," *TR* November 2003). We know how to write good software—it just takes too long, and it's too expensive for the rather trivial consumer products that currently drive the industry. With product cycles shorter than a year and profit margins low or nonexistent, programmers are not permitted to write good code. Now the solution proposed in your article is to get rid of programmers and replace them with machines to do the programming. These programming machines have been touted as the solution now for years, but they can produce coding errors on a grander scale than mediocre human programmers. When such tools finally appear, and accountants and insurance specialists can write their own software, I think we will discover just how bad software can really get.

E. G. Merrill
Daglish, Australia

YOUR ARTICLES ON NEW SOFTWARE paradigms are thought-provoking, particularly the story about Charles Simonyi's efforts. I was surprised, however, to see no mention of visual programming. Visual programming seems like a reasonable way to make the program look like the design. One reason that software projects become difficult is flaws in design. Exposing these flaws early would help, and visual programming could make such flaws more visible.

Beryl Nelson
Tokyo, Japan

TREATING CHRONIC PAIN

THE ARTICLE "STOPPING PAIN" (*TR* November 2003) highlights a major yet only recently acknowledged medical problem: chronic pain. Many biotech companies assume that because blocking activity of peripheral pain neurons is effective in the short term, it will also work for chronic neuropathic pain arising from damage to neurons. But evidence is accumulating that damage and degeneration of peripheral pain-sensing neurons is a major *cause* of neuropathic pain—and

thus unlikely to cure it. Loss of input from pain-sensing neurons causes changes in the spinal cord and brain, as central neurons increase their electrical gain to compensate for fewer incoming peripheral signals. The article ignores an effective treatment technology for neuropathic pain: nerve or spinal-cord stimulators. These implanted electrodes provide long-lasting relief. The mentioned divergence of opinions between biotechs and clinicians/scientists about mechanisms of neuropathic pain may have adverse consequences for investors and businesses, and for patients awaiting better treatments. Biotech research needs more input from clinicians and patients—the ultimate authorities about disease.

Anne Louise Oaklander
Harvard Medical School
Boston, MA

RFID: TRULY INNOVATIVE

WE WERE BEWILDERED BY MICHAEL Schrage's column "Little Bang for the RFID Buck" (*TR* November 2003). First of all, the casual statement that there's a huge difference between customers who invest in innovation to save money and those who invest to make money runs counter to the principles of modern finance. In fact, one of the clearest ways to add value in a company is by reducing costs. Radio frequency identification (RFID) has the potential for massive cost savings, which can be illustrated by a back-of-the-envelope analysis, as the author himself mentions. Second, the article surmises that consumers will not benefit from RFID. In fact, as more and more companies reap the benefits of RFID in a competitive environment, they will pass most of the cost savings on to consumers. RFID also has implications for food safety, quality control, counterfeit prevention, and homeland security. Third, the article fails to note the Auto-ID Center's public policy, which includes explicit support of consumer notice and consumers' ability to deactivate, destroy, or discard the RFID tag. On balance, the article seems to run counter, at a gut level, to innovation. Isn't innovation the hallmark of *Technology Review*?

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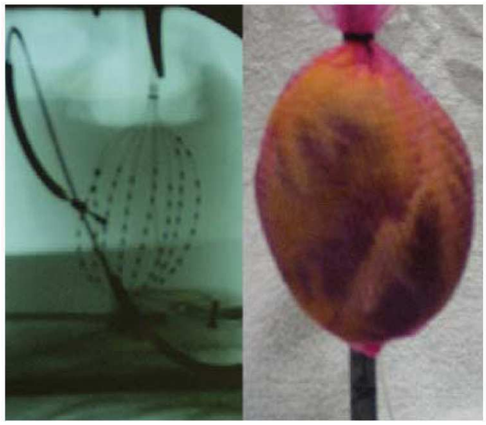
CORRECTION: Due to an editing error, Joe Chung's column ("Lunch Is on Me," *TR* December 2003/January 2004) indicated that Ovation Products has received investments from Polaris Venture Partners and Cardinal Partners. In fact, like all the companies that Chung will profile in his columns, Ovation has yet to raise any venture investment.

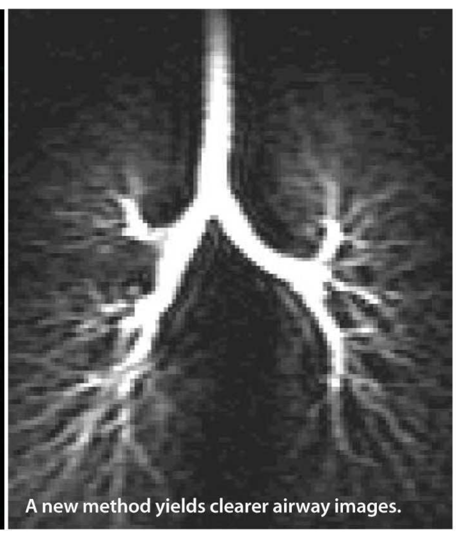
SHOCKING GENES



Electrodes inside (left) and outside a human heart.

GENE THERAPY HOLDS PROMISE for treating diseases from cystic fibrosis to diabetes. But safely and effectively delivering genes to the cells that need them has been the field's biggest obstacle. Luyi Sen, a cardiologist at the University of California, Los Angeles's David Geffen Medical School, has a technique that could help: she uses small electric shocks to "push" the genes into cells. Scientists have long employed electric shocks to transfer genes into cells in research labs, but the voltages used would damage whole organs. Sen has lowered those voltages by placing electrodes in contact with a patient's tissues. She arranges 32 to 128 electrodes in a "basket" on a catheter or endoscope and threads the tube through blood vessels into the interior of an organ, where the basket is expanded. Therapeutic genes in solution are fed through another vessel, and tiny electric jolts induce cells to take up the genes. In tests on rabbit hearts, genes have been transferred at up to 75 percent efficiency. Today's most popular gene delivery method, viruses made noninfectious, has top rates of only 70 percent and can cause dangerous immune reactions. Several firms have expressed interest in manufacturing Sen's devices.

Current lung scans often turn out fuzzy.



A new method yields clearer airway images.

LIGHTING UP LUNGS

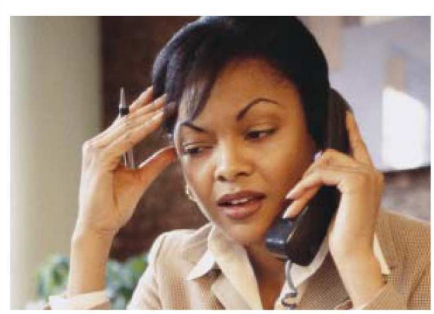
MAGNETIC-RESONANCE IMAGING HAS DRAMATICALLY IMPROVED DOCTORS' views of the body. But obtaining clear pictures of the lungs has been a struggle. Now researchers at Harvard Medical School have found a way to make these MRIs crystal clear. In an experimental procedure for performing lung MRIs, a patient takes a breath of polarized helium, which naturally spreads through the lungs' branching airways to the oxygen-filtering sacs at their ends. The gas becomes magnetized and highlights the airways in the scan—but the sacs light up, too, which largely blocks the view. The Harvard researchers have improved upon this method: *hyper*polarized helium is administered as the patient inhales for several seconds, while the MRI scanner records a series of images of the gas spreading through the airways. Radio-frequency pulses from the scanner also depolarize the helium that reaches the air sacs—producing clear images of just the airways. The technique could aid diagnoses of asthma and cystic fibrosis. Durham, NC-based startup Polarean is commercializing polarization systems that will enable these types of MRIs; the company plans to pursue FDA approval starting in 2005.

DATA REMEDY

One PC at work, another at home, a laptop on the plane, and a personal digital assistant in the taxicab: keeping all that data current and accessible can be a major headache. Randolph Wang, a Princeton University computer scientist, hopes to relieve the pain with one mobile device. Designed to provide anytime, anywhere access to all your files, the device stores some data, but its main job is to wirelessly retrieve files from Internet-connected computers and deliver them to any computer you have access to. Wang's prototype is a PDA with both cellular and Wi-Fi connections, but the key is his software, which grabs and displays the most current data stored on multiple computers. Wang has tested his prototype with more than 40 university and home computers on and around the Princeton campus. He eventually wants to shrink the device down to the size of a wristwatch to make carrying it a snap.

ACCENTUATE THE POSITIVE

THE AUTOMATED TELEPHONE CALL centers companies use to reduce costs can drive customers crazy. A way to spot impatience in callers' voices—and transfer them to human operators before they hang up—could ease the frustration. Shri Narayanan and Chul Min Lee at the University of Southern California have developed a system that distinguishes irritated from normal speech with up to 85 percent accuracy. Their program identifies specific acoustic features of speech that indicate stress, such as the pitch, energy, and duration of speech sounds, as well as word content and contextual information. The system "learned" what to look for through training on nearly 1,400 real phone calls. The team hopes to improve the software's accuracy but says it could already benefit companies.



Software can recognize callers' annoyance.

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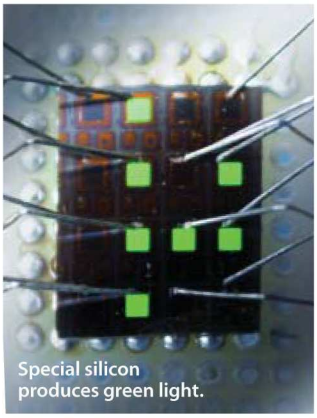
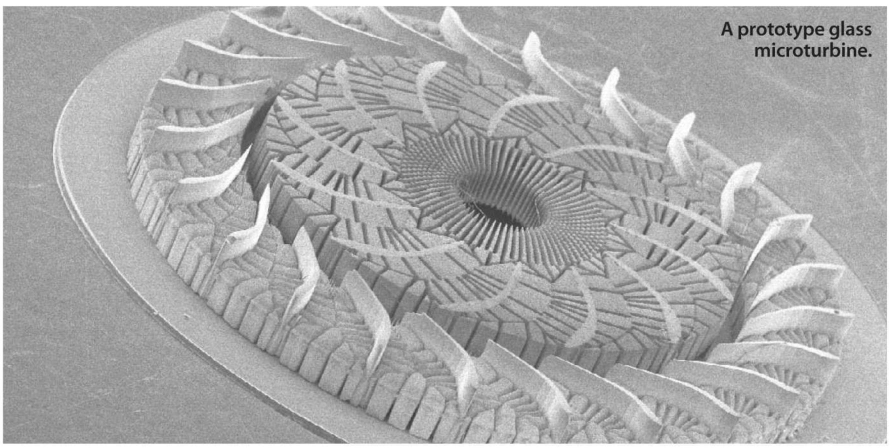

Special silicon produces green light.

GLOWING SILICON

OPTICAL CHIPS THAT TRANSMIT DATA ON BEAMS OF LIGHT PROMISE FASTER AND MORE reliable computing, but they have not caught on widely because they must use expensive, exotic semiconductor materials to emit light: plain silicon won't do the job. Now a research group led by physicist Salvatore Coffa at STMicroelectronics, headquartered in Geneva, Switzerland, has developed an all-silicon chip that combines both optics and electronics. Parts of the silicon are mixed with special rare-earth elements, which enables them to generate light about 100 times more efficiently than any previous silicon device, according to Coffa. The one-millimeter-square device uses light beams to talk to other chips. The STMicroelectronics chip's first applications will be in telecommunications and biomedical devices, but it could eventually enable new processors for high-end computers and cheaper lasers and plasma displays. Potential customers will test the chip by the middle of 2004, says Coffa, and it could be incorporated into "billions of devices" by 2007.


A prototype glass microturbine.

GLASS MICROMACHINES

FROM LABS-ON-A-CHIP THAT MIX TINY AMOUNTS OF FLUIDS IN BIOMEDICAL assays to the miniature radios envisioned for future cell phones, a growing number of devices require microscopic parts. More-complex parts are usually made, layer by layer, atop wafers of silicon. Now Invenios, a startup in Santa Barbara, CA, is experimenting with a faster, cheaper process that can create 3-D shapes as small as a cubic micrometer with a single pass of a laser. The technique, invented at Aerospace, an El Segundo, CA-based defense contractor, starts with a special kind of glass whose atoms are in a jumbled, unordered state. Guided by computer-aided-design files, a laser beam strikes certain areas inside the glass, displacing the atoms' electrons. Then, when heated, the treated parts of the glass form ordered, crystalline structures. The crystalline material is etched away by acid, leaving behind glass structures such as tiny turbines, microfluidic valves, or optical waveguides for fiber-optic systems. Thousands of millimeter-scale components could fit on a single wafer and could cost as little as 30 cents each in volume.

TISSUE TESTER

Tissue engineers are working on ways to grow skin, cartilage, and bone in the lab so that injury victims don't have to rely on replacement tissues extracted from donors or from their own bodies. One obstacle researchers face is that while they can easily examine the health of cells on a tissue's surface, checking whether the cells deep inside are thriving or dying remains tricky. Chemical engineer Zhanfeng Cui of Oxford University has developed a small polymer probe that determines the cells' health instantaneously. A fraction of a millimeter in diameter, the needlelike probe can be inserted into growing tissue and measures the levels of certain key substances, such as nutrients or cellular waste products. The probe is made of a porous membrane that the target molecules can pass through; the number of molecules that enter correlates with their concentration in the tissue. Cui hopes to license the technology for commercial development or find investors for a startup to manufacture the probes. As commercial products, the probes could speed the development of tissue engineering—delivering new hope to desperate patients.

GOOD VIBRATIONS

TINY TREMORS IN YOUR OFFICE OR CAR COULD SOON POWER ALL sorts of small gadgets, thanks to MIT materials scientists Robert O'Handley and Jiankang Huang. The pair have developed devices less than five centimeters long that transform slight vibrations into usable electricity. Inside, a spring links a magnet and a coil of copper wire; minuscule movements of the magnet and coil produce an electric current. Attached to a rattling duct or water pump, the device generates a few milliwatts of power—enough to drive, say, a temperature sensor. The duo cofounded Ferro Solutions in Cambridge, MA, which is partnering with Cambridge, MA-based Millennial Net to build battery-free wireless sensors for factory and building management. Other anticipated applications include energy sources for automotive sensors, micromotors in printers, and even cell phones.

A new device uses vibrations to power a sensor.

COURTESY OF FERRO SOLUTIONS (VIBRATIONS); COURTESY OF THE AEROSPACE CORPORATION (MICROMACHINES); COURTESY OF STMICROELECTRONICS (SILICON)

VIPs: Virally Interactive Pixels

I WAS WRONG. UTTERLY. I HONESTLY BELIEVED digital-camera cell phones were a silly, bandwidth-hogging gimmick more appropriate to the giggling-Japanese-schoolgirl market than to harried American motor-mouths. Foolish me. ■ Camera phones threaten to surpass DVD players as the personal technology devices with the fastest-growing market in history. Analysts estimate that 57 million camera phones were sold worldwide in 2003, compared to 44 million stand-alone digital cameras. Nokia says most of its new phones will have built-in cameras. Say "cheese."

Note to self: start paying more attention to Japanese schoolgirls as global technoculture's beta site.

Second note to self: there is *always* a mass market in instant gratification. It's clearly worked for digital music and handheld games. Edwin Land anticipated the appeal of instant photography more than 50 years ago. Marrying that sensibility with mobile transmission is a no-brainer. I should have known that *Hey! Look at this right now!* is just as powerful an interpersonal message as *Hey! Listen to me right now!*

Being wrong about successful innovation forces you to look at it with new wariness and respect. The success of camera phones leads me to suspect that images will matter far more than voice in spreading the next generation of "instant gratification" telecommunications innovations. I like what I could see.

What I want—what I need—is a camera phone that would let me take a picture of an article in a newspaper *and translate it into a machine-readable form* that I could send on to a colleague, a client, or, indeed, myself. In other words, I want my mobile camera/phone to be a handheld scanner with built-in optical character recognition.

If the phone keypad would let me highlight, delete, or otherwise edit the text document I'm sending, that would be even better. Would I settle for sending it to my laptop for editing? Sure. The point here is to give me more reasons to take more types of pictures.

Camera phones can be channels for viral marketing, where consumers convert their friends to new products simply by using them.

Instant photography, however, is an insufficient metaphor. My mobile should be marketed as a general input/output device. If it works well enough, it will do away with the traditional boundary between "photos" and "scans."

But wait! I already have a $79 key-chain memory device that plugs into the USB ports on my computers and lets me carry up to half a gigabyte of data between home and work. This accessory could double as the connection device between my camera phone and my PC. It would be terrifically cool if I could take pictures and plug my key chain into my camera phone to download them, then transfer them to my home computer. It would be equally cool if I could copy an entire photo album to my key chain, then use the phone to sort through it and send whichever picture—or document—I wished. In other words, I want my phone to have at least one USB port.

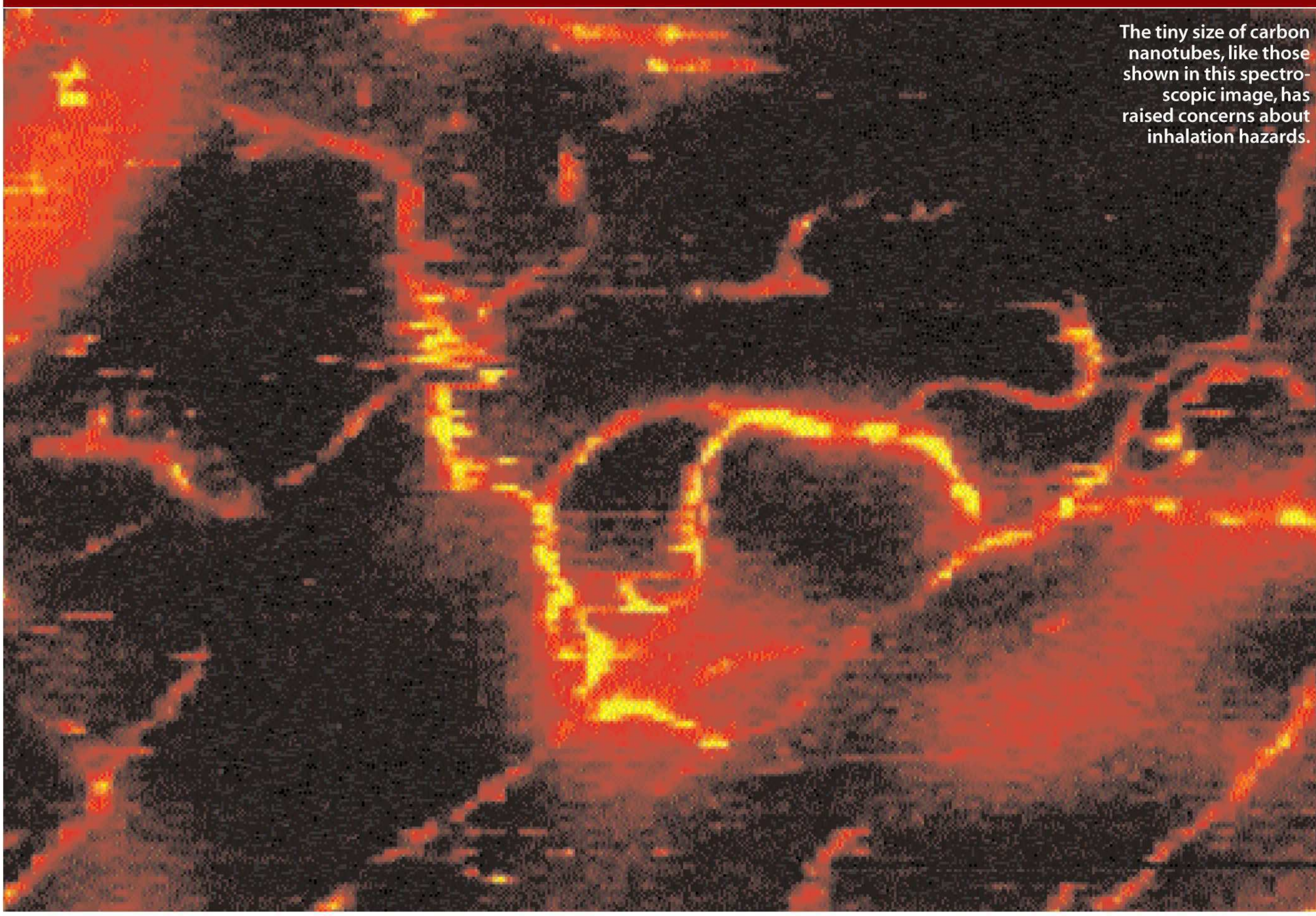
Yes, I know about the Handspring Treo and its knockoffs, which attempt to blend phone, camera, datebook, e-mail, and Web-surfing capabilities into a single form-factored box. But while these technologies foster certain forms of "instant interconnectivity," they're not yet tailored to supply the kind of immediate gratification that's making simple camera phones so popular.

In the same way a camera phone makes it easy to "snap & send," the next generation of visualization innovation could come from making it ever easier to "snap & back up" or "snap & scan" or "scan & edit." Think of mobile phones as a channel for viral marketing, where consumers convert their friends to new products simply by using them. Camera phones therefore become digital platforms for "VIPs"—Virally Interactive Pixels. Both mobile manufacturers and service providers have a powerful incentive to promote VIPs as the messaging medium of the future. In the same way people trade games wirelessly and respond to voice and wireless text messages, they should be able to respond to VIPs.

Increasingly ubiquitous VIP interconnectivity should inspire different kinds of communications behaviors. My bet on a "metric of the future" is "instant forwarding": that is, in the same way people forward jokes and URLs on mailing lists, they will immediately forward some VIPs they receive on their mobiles. Will they send these goodies to their own PCs? Or will they forward them to the mobiles and/or e-mail addresses of friends and colleagues? If I'm running a cellular service, I have to believe that the growth of "IF" for VIPs will become one of my critical indicators of customer use.

Then again, I'd feel more confident about betting on IF-VIPs if I knew that mobile scan & edit—and not just snap & send photography—was capturing the attention of Japanese schoolgirls. TR

Michael Schrage is a consultant and researcher who writes widely about innovation.



The tiny size of carbon nanotubes, like those shown in this spectroscopic image, has raised concerns about inhalation hazards.

COURTESY OF THE INSTITUTE OF OPTICS, UNIVERSITY OF ROCHESTER

Nano's Safety Checkup

Concerns over particle dangers could slow nanotech's growth. **BY IVAN AMATO**

EVEN AS THE PACE OF nanotechnology research accelerates in labs around the world, a few early studies have raised concerns that tiny man-made particles might pose threats to human health or the environment. While the extraordinary properties of nanoparticles (those smaller than 100 nanometers, the size scale of viruses and even individual molecules) could enable everything from extremely sensitive diagnostic tools to superstrong materials, those same properties might also allow them to penetrate deeper into the lungs, pass more readily through skin, or linger longer in the environment as pollutants—effects that could trigger new regulations.

A collective effort to gather more information is now under way among corporate, academic, and government researchers hoping to get a clearer understanding of whether nanoparticles really do present any dangers. The stakes could hardly be higher. Common items—including some sunscreens and tennis balls—already contain nanoparticles, and some estimates hold that global nanotech-based production will exceed $1 trillion within 15 years. Environmental groups are beginning to warn about potential dangers; the activist organization ETC Group, for one, is actively lobbying for a research moratorium.

The debate is hampered by a dearth of data. "The lack of technical data on the topic provides fertile ground for both nanotechnology proponents and skeptics alike to make contradictory and sweeping conclusions about the safety of engineered nanoparticles," says Vicki L. Colvin, a chemist and director of the Center for Biological and Environmental Nanotechnology at Rice University in Houston. But over the next several years, she says, useful data should be on hand.

One key question is what happens to nanoparticles in the environment. Researchers at Rice are currently conducting studies of how soccer-ball-shaped carbon molecules known as buckyballs—a potential ingredient of everything from new contrast agents for medical imaging to active layers in fuel cells—affect bacteria and simple organisms like worms. In a separate study they are exploring whether buckyballs tend to move up the food chain. In addition, Rice researchers are examining how effectively buckyballs, which are extremely stable and robust, absorb toxic materials; binding to buckyballs could potentially make the toxins themselves more chemically stable, or enable them to travel farther through air or water.

Other studies are examining the effects of inhaling nanoparticles, an issue of particular concern for workers in laboratories or factories where nanoparticles are being used. In animal experiments last year, researchers at DuPont in Wilmington, DE, found that single-walled carbon nanotubes—which show promise for use in nanoelectronics and ultrastrong materials—ended up deep in the tiny air sacs of rats' lungs, where they caused lesions indicative of toxicity. In 15 percent of the rats, the carbon nanotubes aggregated into lethal, suffocating clumps. This and other studies by David Warheit, a DuPont toxicologist, indicate that size matters; nanoparticles generally are more toxic when inhaled than larger particles of the same materials.

Warheit says his experiments so far have been relatively crude; he essentially squirts nanoparticles into the rats' tracheas with a syringe. Now, Warheit is working on developing more realistic exposure methods for assessing risks and identifying a handful of nanoparticles that can serve as test models for nanomaterials in general. However, he says, don't expect conclusive results for a few more years.

Amid scant data on environmental and health effects of tiny particles, plans for more and better studies are under way.

Regulatory agencies are also beginning to get involved. The U.S. Environmental Protection Agency is now in the midst of selecting about a dozen studies to fund under a $4 million solicitation for research proposals issued last July, says Barbara Karn, a coordinator of the funding program. The goal is to investigate health and environmental effects of nanomaterials, but the selection process is still in an early stage, and the research itself will take years, Karn says.

Meanwhile, a key question the agency faces is how existing protocols for regulating new chemical substances—such as those established under the Toxic Substances Control Act—apply to nanoparticles. The law governs certain chemicals but doesn't distinguish among size scales; the issue is whether nanomaterials warrant the creation of a new category simply by dint of their size.

Kent Anapolle of the EPA's Office of Pollution Prevention and Toxics says the EPA is relying on existing protocols, but is in the process of determining whether they are adequate. If new data and experience suggest they aren't, he notes, then "we can craft a regulatory action any way we see fit to mitigate a risk." The U.S. Food and Drug Administration is also relying on existing protocols for nanoscale zinc oxide and titania particles in consumer products ranging from sunscreens to cosmetics.

Europe is also in the early stages of grappling with the issue of nanoparticle safety. Last year, the European Union didn't fund a proposed four-year program that would have created a pan-European collaboration of specialists assessing the workplace risks of airborne nanoparticles. That proposal could still be funded; meanwhile, some individual countries are pushing ahead. The U.K. has commissioned the Royal Society and the Royal Academy of Engineering to complete by this spring a preliminary study of the risks and benefits of nanoparticles and to specify the research that is needed to enable informed regulatory decisions.

The long-term hope is that nanotechnology will open vast commercial opportunities. But getting the hard data on the safety of many of the different nanomaterials in development will be a critical step. TR

SOME EFFORTS AND PROPOSALS ON NANOPARTICLE SAFETY

ORGANIZATION	EFFORT
U.S. Food and Drug Administration; U.S. Environmental Protection Agency (Washington, DC)	Relying on existing protocols to regulate new nanomaterials, while developing data on toxicology, environmental fate, and tissue accumulation
U.K. Royal Society (London, England)	Commissioned a blue-ribbon study to assess the risks and benefits of nanomaterials and make regulatory recommendations
Center for Biological and Environmental Nanotechnology, Rice University (Houston, TX)	Director Vicki Colvin recommended that 5 percent of federal nanotechnology R&D expenditures be devoted to the study of environmental and societal consequences
ETC Group (Winnipeg, Manitoba)	Calling for moratoria on nanotechnology R&D until safety can be established; seeking an international convention to evaluate nanotechnology
Greenpeace Environmental Trust (London, England)	Calling for far more research on nanotechnology's environmental impact, but not endorsing moratoria

BIOTECH

Digestive Diagnostics

Meet another installment in biotech's "-omics" series: metabolomics. While doctors have been charting levels of individual metabolites like cholesterol for years, a growing number of researchers are measuring hundreds of metabolites—fatty acids, amino acids, and sugars produced by cells' everyday activities—more systematically. They say this will enable earlier diagnoses of a wide array of diseases and provide a set of new tools for developing safer drugs.

To identify the most meaningful metabolites of the thousands in the body, several companies are making systematic measurements of metabolites in sick and healthy people, hoping to pick out a few dozen, perhaps, that can become critical early markers for diseases, or for toxicity in drugs under development. In some ways, the research is a natural extension of the growing understanding of the body's many different genetic and molecular players, including genes and proteins. "We're just realizing now that we're looking at a small part of the picture by focusing on genomics and proteomics," says Jeremy Nicholson, head of biological chemistry at Imperial College in London, England. Genes, he says, only tell you the potential for something going wrong in the body, and proteins only tell you which genes have been turned on, but metabolites show "real-world changes. They show that something has really happened to the body."

One early payoff could be a better heart disease test. Metabometrix of London is, among other efforts, developing a blood test that would measure various combinations of metabolites—specific fat and cholesterol molecules—using standard chemical analysis tools. Software would then search through a database, comparing that metabolite profile to those of thousands of patients with and without heart disease. This blood test—which the company expects to bring to market in three years—would hopefully allow some people to avoid getting angiograms—the traditional method of diagnosis—which are expensive and invasive. The company, founded by Nicholson and colleagues at Imperial College, is also working on a similar test to diagnose osteoporosis, providing an alternative to x-ray bone-density scans.

The longer-term goal: prevention. J. Bruce German, professor of food science and technology at the University of California, Davis, envisions people getting comprehensive metabolic profiles done during their yearly checkups. Of course, individual metabolites are already commonly tested. But more sophisticated tests could serve as far earlier indicators of impending diseases such as type II diabetes. And with the profiles, patients would get more fine-tuned instructions on how to correct their diets—though it's unlikely they'll ever be spared the lecture to eat healthier and exercise more. **Corie Lok**

MARKETING METABOLOMICS

COMPANY	TECHNOLOGY
Beyond Genomics (Waltham, MA)	Tests for heart disease and other diseases; drug efficacy tests
Lipomics Technologies (West Sacramento, CA)	Toxicity and efficacy tests for drugs for heart disease and other diseases
Metabometrix (London, England)	Tests for heart disease and osteoporosis
Paradigm Genetics (Research Triangle Park, NC)	More-sensitive tests for liver disease
SurroMed (Mountain View, CA)	Tests for autism, heart disease, and other diseases

ENERGY

Alternative to Incineration

Incineration destroys most dangerous components of medical and other hazardous wastes, but even the hottest furnaces still produce nitrogen oxides, dioxins, and toxic ash. After years of industry efforts to develop a versatile noncombustion thermal alternative—one so hot that wastes are transformed into less harmful or even useful gases and glassy solids—a dual-heating system is proving commercially viable.

Developed by Integrated Environmental Technologies of Richland, WA, which is commercializing technology developed partly at MIT, the system recently hit a key milestone. Industrial-gas giant Praxair last fall decided to market the technology to the chemical industry to destroy toxic waste, and in the process create hydrogen. "It effectively eliminates off-site transfer and disposal, typically by incineration, of hazardous wastes," says Gary Storms, commercial-development manager for Praxair in Danbury, CT.

The system combines two tightly controlled heating methods inside a cauldron. In the first, plasma generated by two or more graphite electrodes courses through a stream of incoming waste; in the second, waste is melted through electrical-resistive heating. The combined effect pushes temperatures to 10,000 °C and creates a lava-like soup that gives off gases like hydrogen and carbon monoxide and eventually cools into chunks. Jeffrey Surma, president and CEO of Integrated Environmental Technologies, says the approach "has the ability to tune exactly where we want the input energy to go," helping the system work for differing mixtures of waste. Nick Soelberg, a chemical engineer at the Idaho National Engineering and Environmental Laboratory, calls it "a reasonable alternative to incineration." Other companies including Startech Environmental of Wilton, CT, are also commercializing plasma systems; eventually, perhaps, the incineration era will burn out. **David Talbot**

Waste is melted inside a dual-heating chamber.

Air-powered artificial leg muscles (above) receive instructions from muscle-stiffness sensors (inset).

ROBOTICS

Wearable Devices Add Strength

AT NAGASAKI UNIVERSITY IN Nagasaki-City, Japan, mechanical engineer Shunji Moromugi straps on a pair of what he calls "power pants" and gets to work. Holding a 16-kilogram barbell on his shoulders, he does 90 squats in 90 seconds without breaking a sweat. That's because the pants contain computerized sensors that detect what his legs are doing—deep knee bends—and tubelike artificial muscles, mounted on both sides of the knee, that expand and contract with flows of compressed air. The artificial muscles are attached to a steel brace that spans the thigh and calf; when they lengthen, they extend Moromugi's knee and help him stand more easily.

These power pants might just be the closest thing yet to a realization of long-held visions of mechanical systems that improve the mobility of the elderly and disabled or boost the strength of soldiers and rescue workers. Where previous wearable robots proved cumbersome and hard to control, this latest version—a collaboration between Nagasaki University, the University of Electro-Communications in Tokyo, Japan, and the University of California, Irvine—is smarter and more practical. Robotics experts say it's an important step toward building machines that people will actually use. "This is novel because it's sensing over the entire soft-tissue interface of the body," says Ephrahim Garcia, a mechanical and aerospace engineer at Cornell University and a former program manager at the U.S. Defense Advanced Research Projects Agency. "You need intense amounts of computation to pull it off," he adds.

Indeed, the system's tiny sensors are distributed over the legs and hips to measure signals that muscles give off when they contract. Every few milliseconds, strain gauges and ultrasonic disk-shaped sensors in cuffs around the user's legs measure the stiffness and density of the underlying tissues and communicate wirelessly with a computer that makes sense of the signals—predicting the user's intended movements on the basis of experimental data and mathematical models. Then, like a diligent weight-room spotter, the computer controls the artificial muscles. "We're trying to reduce fatigue and eventually help disabled people," says Maria Feng, a civil engineer at UC Irvine and a collaborator on the project.

The robotic pants are being tested at Nagasaki University for use as a physical-therapy tool for patients confined to bed. The researchers are also testing a mechanical glove that allows a user to pick up a coffee cup just by tensing muscles in his or her upper arm—important for, say, a person who has lost fine motor control due to a spinal injury or cerebral palsy. In the next two years, says Feng, the researchers will work out the remaining bugs and begin widespread testing of the devices in clinics and with patients.

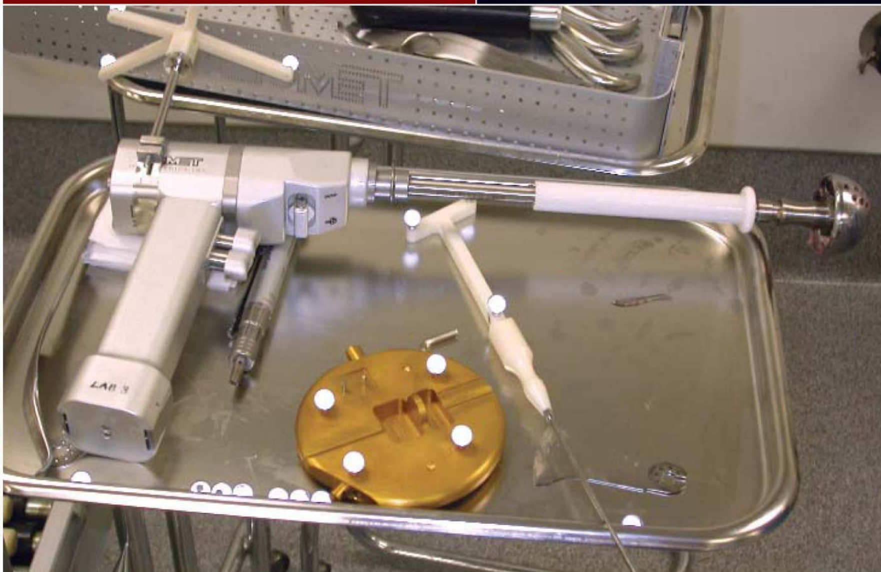
If all goes well, such human-assist machines might hit the market in five to ten years. That's because dozens of robotics researchers are working on related projects, with tens of millions of dollars of funding from DARPA alone. At the University of California, Berkeley, mechanical engineers have built robotic "exoskeletons" that connect to people's legs to help them balance, walk, and run with less effort. The researchers are currently developing a prototype lower-body suit, powered by rocket fuel, that could allow soldiers to move more easily over uneven terrain while carrying heavy equipment.

So who will be the first to actually use such devices? The consensus among the researchers is that physical therapy and rehabilitation will be the initial commercial applications. But that will require streamlining the technology to make it as safe and reliable as possible. It's still too early to say whether the real impact will be felt on the battlefield or in the home. But if the research and development is successful—and wearable robots prove to be good for your health—they may become fashionable to boot. **Gregory T. Huang**

LEADERS IN WEARABLE ROBOTS

RESEARCHER/ORGANIZATION	TECHNOLOGY
Maria Feng, University of California, Irvine (Irvine, CA)	Ultrasonic and kinematic sensing of body movements
Stephen Jacobsen, Sarcos (Salt Lake City, UT)	Exoskeleton to increase speed and strength
Homayoon Kazerooni, University of California, Berkeley (Berkeley, CA)	Powered, computer-controlled exoskeletons
Ben Krupp, Yobotics (Cincinnati, OH)	Strength-enhancing, powered leg braces
François Pin, Oak Ridge National Laboratory (Oak Ridge, TN)	Fuel cells and hydraulics to power wearable robots
Takayuki Tanaka, University of Electro-Communications (Tokyo, Japan)	Artificial muscles for rehabilitation

COURTESY OF MARIA FENG AND SHUNJI MOROMUGI

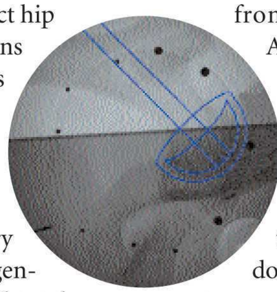


Spherical reflectors on hip surgery tools (above) help doctors see an implant's location (below).

MEDICINE

Hip Checker for Easier Surgery

IF YOU'RE ONE OF THE 300,000 Americans going in for traditional hip replacement surgery this year, you can look forward to an incision 15 to 25 centimeters long, two to three months of waiting before you can take long walks again, and a 1 to 4 percent risk of dislocation. But new technology could make the surgery a lot less onerous. An emerging class of computer navigational systems will allow surgeons to conduct hip replacements through incisions as small as four centimeters and to align implants more accurately. That could mean less pain, faster recovery, and reduced risk of joint failure.



Minimally invasive surgery itself is nothing new. But it generally involves a pinpoint of light at the end of an endoscope that guides a surgeon's tools during a very localized procedure, like gall bladder removal or a heart bypass. With major orthopedic procedures, surgeons need a far wider view. To provide that view during hip surgery, several companies, including Smith and Nephew Orthopedics of Memphis, TN, and Biomet of Warsaw, IN, in partnership with z-kat of Hollywood, FL, are bringing guidance systems to market.

A Smith and Nephew system is typical. It starts with half-centimeter spherical reflectors affixed to the patient's bones and to the surgical instruments. A conventional CT scan then provides a map of the pelvic area. During surgery, an infrared-light-emitting camera bounces light off the reflectors and registers their position. Software produces an image that shows the surgeon where his or her tools are and displays precise measurements.

Smith and Nephew received approval from the U.S. Food and Drug Administration last year for this hip surgery system; 25 surgeons worldwide are testing it on humans. Z-kat and Biomet, among other companies, are in advanced stages of the approval process. Not only do better imaging systems reduce trauma, but the precise measurements they provide will help less experienced surgeons do a better job and "make results more consistent across patients," says Anthony DiGioia, a surgeon and director of the Institute for Computer Assisted Orthopaedic Surgery at the Western Pennsylvania Hospital in Pittsburgh.

Hip surgeries are the latest guided orthopedic procedures; versions for spine and knee surgeries already exist. While these systems still must become more user friendly, "there's no doubt that they will be mainstream," DiGioia says. **Corie Lok**

SOFTWARE

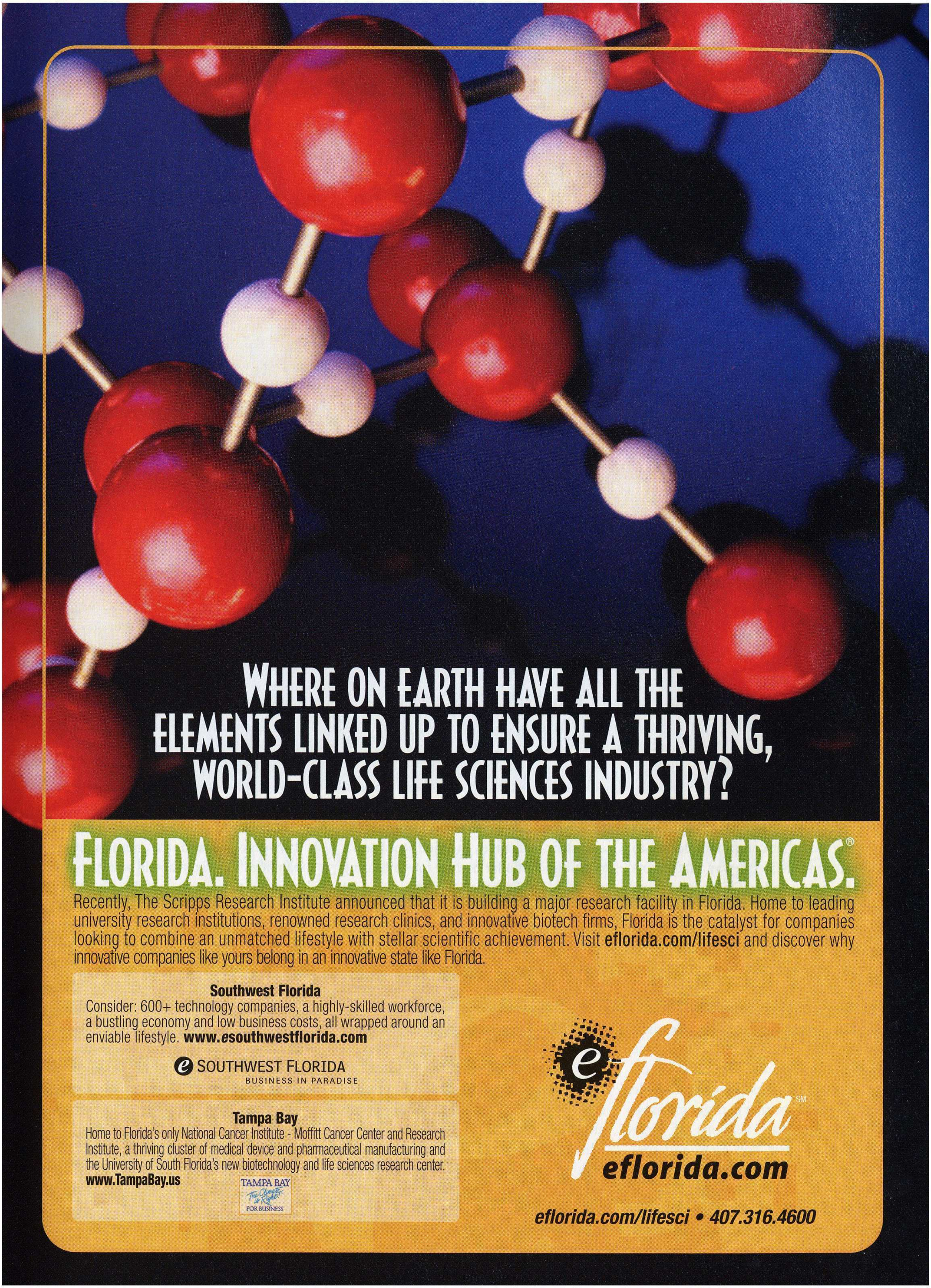
Old Logs, New Tricks

Today, at universities and companies alike, everything from broken printers to failed Web transactions generates computer error messages. And while technicians pore over reams of system status "logs"—text files that document what's happening in the network—everyone else loses precious time trying to access disconnected file servers, Internet links, and e-mails.

Now, a new tool is emerging to break the logs' logjam. Researchers at San Jose, CA-based Cisco Systems and IBM Research in Yorktown Heights, NY, have developed software that scours logs, converts them to a standard format, and automatically extracts important information. The key is machine-learning algorithms that let system managers teach computers new tricks. If a log states that, say, a server is down, the system manager flags "down" as a keyword and instructs the software to search for the server name, time of failure, and any ripple effects in the network. The software can then apply this instruction to new messages, reducing the need for human intervention. "This is an important step in automating networks," says Cynthia Hood, a computer scientist and expert in network management at the Illinois Institute of Technology. "Everyone knows how much money is spent on configuring networks and keeping them running."

Large companies like Toshiba, Hewlett-Packard, and Computer Associates are currently evaluating the technology. This could mean users of computer networks will soon encounter fewer disruptions—for shorter durations. The bottom line, says Alan Ganek, vice president of IBM's autonomic-computing initiative, is that identifying problems quickly, or even before they occur, lets users "focus on their business and not their infrastructure." It all starts with teaching old logs new tricks. Gregory T. Huang

COURTESY OF Z-KAT INC. AND BIOMET INC. (SURGERY)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The Robots Are Here

FOR YEARS WE'VE HEARD THE PREDICTION THAT "the robots are coming." Now, they've actually arrived. They permeate our homes as toys like Lego Mind-Storms and the Furby. Robotics graduate programs are well established at many universities, with undergraduate programs starting to appear. Reconnaissance bots roam with U.S. troops in Afghanistan and Iraq. And we've started to see home cleaning robots in stores and advertised on TV.

I've staked my own financial security on the success of some of these emerging robot products. The company I co-founded, iRobot, formerly housed above a Somerville, MA, strip mall, recently moved to offices many times as large, thanks in part to sales of the Roomba robotic vacuum cleaner and PackBot military robot. For a while during the dot-com boom, I was even helping manage a venture capital firm that funds robotic startups. Like all VC firms, it's seen some of its investments disappear, while some are still growing.

I am convinced robots today are where computers were in 1978. That's about the year that computers started to appear around us in the way that robots are cropping up today. Of course, it was another 15 years before computers truly became pervasive in our lives. I think that 15 years from now, robots will be everywhere, as e-mail and the Web are now.

Continued improvement in robotic navigation is one key to this broad future. The lawn-mowing robots, cleaning robots, and military reconnaissance robots that are on the market today do their specialized tasks almost as a side effect of their primary programming: navigation. Robotic versions of large farming equipment, golf carts, and specially built supply mules for the military—all under development—are likewise primarily navigation machines. No doubt many other navigation-based robots will become common in the next few years. From what I see at university labs, we already have in hand many of the scientific advances needed to fuel a multibillion-dollar market for navigating robots. Development at iRobot and at other companies is bringing down costs.

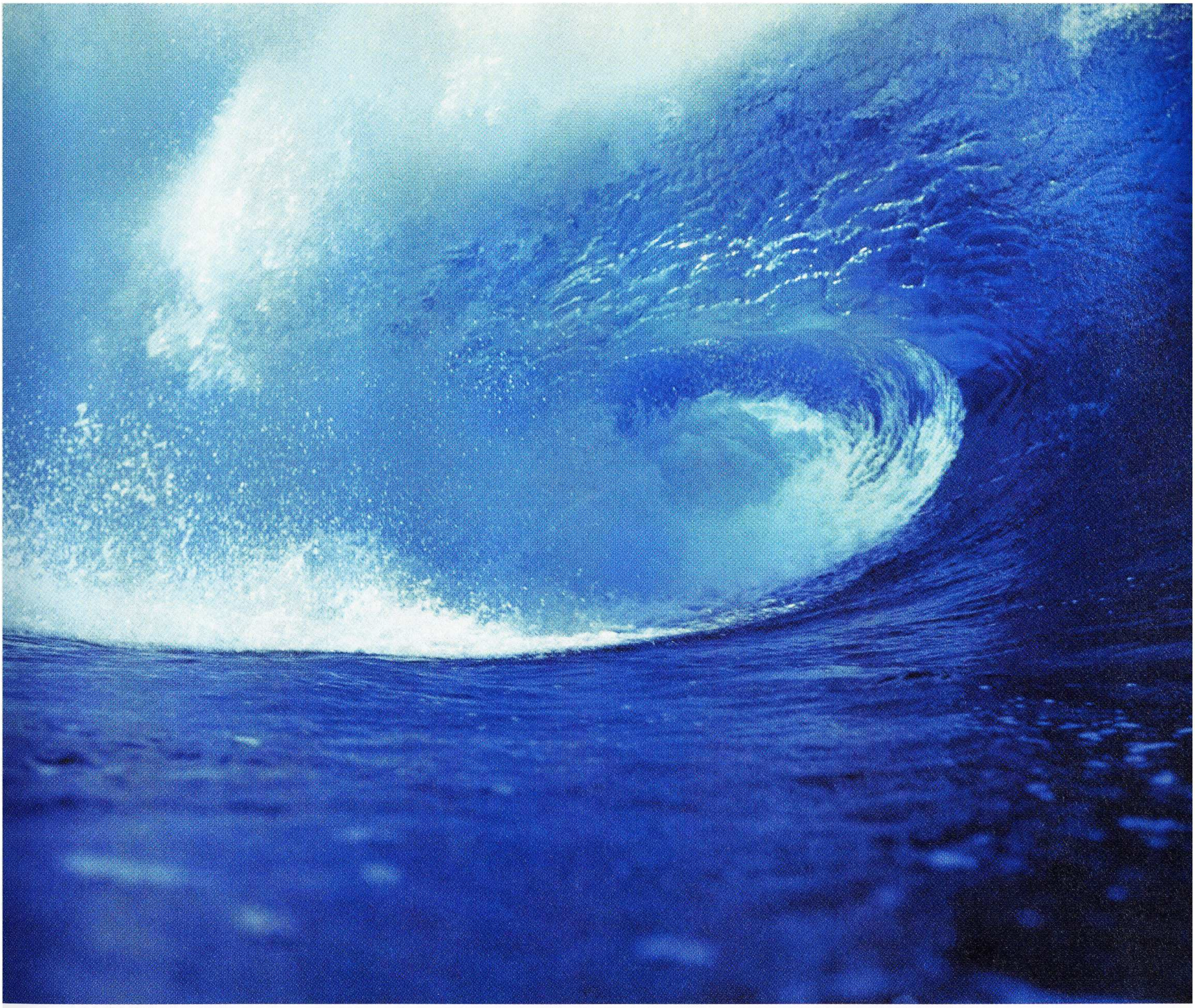
Today's robots will likely create billion-dollar markets, but dexterous ones could reorder global immigration and labor patterns.

But we're also just a couple of research advances away from even bigger growth in a whole new set of markets—growth that will look like what happened in the computer industry over the last 25 years. Take farming. Agriculture in Western Europe and North America relies on vast numbers of migrant laborers to manipulate individual plants. Polish laborers flock to Germany to push dirt up around asparagus to make the spears white. North Africans travel to Italy to pick grapes. And workers from Latin America toil on farms across the United States. All these workers use their eyes to identify the plants and their locations and their hands to manipulate them. In short, a multibillion-dollar market awaits robots that perform these kinds of tasks. Such markets will likely emerge first in Japan, where far higher labor costs make the economics more compelling. Same goes for a broad array of manufacturing jobs. Fabricating home appliances, toys, clothes, and electrical goods requires visual perception coupled with manual dexterity. This could be yet another multibillion-dollar robot market.

True, robots today are still not very good at either recognizing generic objects or readily manipulating them. But Moore's Law has been very, very helpful in chipping away at both problems. Computer vision, while still lagging far behind the average two-year-old, is getting less fuzzy. For example, programs in the lab have gotten very good at tracking motion and recognizing faces. And right now our robots are not particularly adept at grasping objects with varying sizes, shapes, and surface properties. But new sensors enabled by microelectromechanical systems and nanotechnologies—and fueled by plenty of embedded computational horsepower—make the time ripe for researchers to tackle robot dexterity, too. It will help that military funding for advanced information-systems research is likely to shift from navigation to logistics and resupply—which will require better robotic vision and dexterity.

Robots with the vision capabilities of a two-year-old and the manipulation capabilities of a six-year-old will be more disruptive to our way of life than any robot portrayed by the governor of California. They will reorder the world labor markets that have developed over the last 50 years. They will change immigration patterns and the massive shift of labor from developed to developing countries. But the most important impact might well be on elder care: caregiving robots could help us weather the tsunami of aging baby-boomers about to submerge the economies of Europe, North America, and Japan. But more on *that* in a later column. For now, suffice it to say: the robots are here. TR

Rodney Brooks is director of MIT's Computer Science and Artificial Intelligence Laboratory.



10 EMERGING TECHNOLOGIES THAT WILL CHANGE YOUR WORLD

With new technologies constantly being invented in universities and companies across the globe, guessing which ones will transform computing, medicine, communication, and our energy infrastructure is always a challenge. Nonetheless, *Technology Review*'s editors are willing to bet that the 10 emerging technologies highlighted in this special package will affect our lives and work in revolutionary ways—whether next year or next decade. For each, we've identified a researcher whose ideas and efforts both epitomize and reinvent his or her field. The following snapshots of the innovators and their work provide a glimpse of the future these evolving technologies may provide. **PHOTOGRAPH BY DENNIS KLEIMAN**

In 10 years, everyone may have universal-translation software on their handheld or cell phone.
—YUQING GAO

YUQING GAO

Universal Translation

Yuqing Gao is bilingual—and so is her computer. At IBM's Watson Research Center in Yorktown Heights, NY, the computer scientist, role-playing a doctor, speaks Mandarin Chinese into a personal digital assistant. In a few seconds, a pleasant female voice emanating from the device asks, in English, "What are your symptoms?" Gao's system, designed to help doctors communicate with patients, can be extended to other languages and situations. The ultimate goal, she says, is to develop "universal translation" software that gleans meaning from phrases in one language and conveys it in any *other* language, enabling people from different cultures to communicate.

Gao's work is at the forefront of escalating efforts to use mathematical models and natural-language-processing techniques to make computerized translation more accurate and efficient, and more adaptable to new languages. Distinct from speech recognition and synthesis, the technology behind universal translation has matured in recent years, driven in part by global business and security needs. "Advances in automatic learning, computing power, and available data for translation are greater than we've seen in the history of computer science," says Alex Waibel, associate director of Carnegie Mellon University's Language Technologies Institute, which supports several parallel efforts in the field.

Unlike commercial systems that translate Web documents word by word or work only in specific contexts like travel planning, Gao's software does what's called semantic analysis: it extracts the most likely *meaning* of text or speech, stores it in terms of concepts like actions and needs, and expresses the same idea in another language. For instance, the software translates the statement "I'm not feeling well" by first deciding that the speaker is probably sick—not suffering from faulty nerve endings; it then produces a sentence about the speaker's health in the target language. If enough semantic concepts are stored in the computer, it becomes easier to hook up a new language to the network: instead of having to program separate Chinese-Arabic and English-Arabic translators, for instance, you need only map Arabic to the existing conceptual representations.

But it's easier said than done. Spoken-word translation requires converting speech to text, making sense of that text, and then using speech synthesis technology to output the translation. "Building a system for understanding text is more complex than building an atomic bomb," says Sergei Nirenburg, a computer scientist at the University of Maryland, Baltimore County, who pioneered efforts in machine translation in the 1980s. In addition, a practical system must adapt to speech recognition errors, unusual word combinations, and new situations—all automatically.

To address those challenges, Gao's team at IBM combined semantic analysis with statistical algorithms that enable computers to learn translation patterns by comparing streams of text with translations done by humans. As part of an initiative by the U.S. Defense Advanced Research Projects Agency, Gao's team developed Chinese-English translation software for a laptop computer and more recently adapted it to run on a PDA. "You can talk about a lot of different things. The system handles daily conversational needs," says Gao. It has a vocabulary of a few thousand words and worked with 90 percent accuracy in test conversations about medical care and logistics.

"The IBM system is impressive. I see them as setting the bar for the whole program," says Kristin Precoda, director of the Speech Technology and Research Laboratory at SRI International in Menlo Park, CA. Within the same DARPA initiative, Precoda's group has created a more specialized translation device: a one-way talking phrase book developed in collaboration with Middletown, RI-based Marine Acoustics that has been used by U.S. soldiers in Afghanistan, Iraq, and other countries to ask residents specific questions about medical care and many other topics.

While these prototypes look promising, making them practical will require more testing and programming. By late 2004, says Gao, the technology will be "robust and ready" for deployment; IBM is already in discussions with potential partners and customers. Eventually, universal translation could make business meetings, document research, and surveillance easier, while opening doors to international commerce and tourism. "In 10 years, everyone may have this on their handheld or cell phone," says Gao. At which point communicating in a new language could be as easy as plug and play. **GREGORY T. HUANG**

OTHER LEADERS
in Universal Translation

:BONNIE DORR
University of Maryland
(College Park, MD)
Computerized translation of Web documents

:KEVIN KNIGHT
:DANIEL MARCU
Language Weaver
(Marina del Rey, CA)
Statistical translation of text

:LORI LEVIN
:ALEX WAIBEL
Carnegie Mellon University
(Pittsburgh, PA)
Text and speech translation

:KRISTIN PRECODA
SRI International
(Menlo Park, CA)
Portable speech translators

:ACE SARICH
Marine Acoustics
(Middletown, RI)
Handheld phrase translators

:SEIICHI YAMAMOTO
Advanced Telecommunications Research Institute International, Spoken Language Translation Research Labs
(Kyoto, Japan)
Speech recognition and translation

RON WEISS

Synthetic Biology

Perched on the gently sloping hills of Princeton University's brick and ivy campus, **Ron Weiss**'s biology laboratory is stocked with the usual array of microscopes, pipettes, and petri dishes. Less typical is its location: crammed into the Engineering Quadrangle, it stands out among the electrical and mechanical engineering labs. Yet it's an appropriate spot for Weiss. A computer engineer by training, he discovered the allure of biology dur-

Synthetic biology will enable an array of applications in the future that we cannot even imagine today. —RON WEISS

DENNIS KLEIMAN

ing graduate school—when he began programming cells instead of computers. In fact, he began to program cells as if they *were* computers.

Weiss is one of just a handful of researchers delving into the inchoate field of synthetic biology, assiduously assembling genes into networks designed to direct cells to perform almost any task their programmers conceive. Combined with simple bacteria, these networks could advance biosensing, allowing inspectors to pinpoint land mines or biological weapons; add human cells, and researchers might build entire organs for transplantation. "We want to create a set of biological components, DNA cassettes that are as easy to snap together, and as likely to function, as a set of Legos," says Tom Knight, an MIT computer-engineer-cum-biologist, and the graduate advisor who turned Weiss on to the idea.

Researchers trying to control cells' behavior have moved beyond proof of concept, creating different genetic "circuits"—specially devised sets of interacting genes. James J. Collins, a biomedical engineer at Boston University, created a "toggle switch" that allows chosen functions within cells to be turned off and on at will. Michael Elowitz, a professor of biology and physics at Caltech, and Stanislas Leibler of Rockefeller University have created another circuit that causes a cell to switch between glowing and nonglowing phases as levels of a particular protein

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change—acting as a sort of organic oscillator and opening the door to using biological molecules for computing. Together with Caltech chemical engineer Frances Arnold, Weiss himself has used "directed evolution" to fine-tune the circuits he creates, inserting a gene network into a cell, selectively promoting the growth of the cells that best perform a selected task, and repeating the process until he gets exactly what he wants. "Ron is utilizing the power of evolution to design networks in ways so that they perform exactly the way you want them to," says Collins.

Weiss has also designed sophisticated cellular systems without directed evolution. In one project, sponsored by the U.S. Defense Advanced Research Projects Agency, he has inserted a genetic circuit into normally nonsocial bacteria that enables them to communicate with each other by recognizing selected environmental cues and emitting a signal in response. He's working on another group of genes he calls an "algorithm," which allows the bacteria to figure out how far away a stimulus is and vary their reactions accordingly—in essence, creating a living sensor for almost anything. Spread bacteria engineered to respond to, say, dynamite, across a minefield, and if they're particularly close to a mine, they fluoresce green. If they're a little farther away, they fluoresce red, creating a bull's-eye that pinpoints the mine's location.

The most ambitious project Weiss has planned—though the furthest from realization—is to program adult stem cells. In the presence of the correct triggers, these unspecialized cells, found in many tissues in the body, will develop into specific types of mature cells. The idea, says Weiss, is that by prompting some cells to differentiate into bone, others into muscle, cartilage, and so on, researchers could direct cells to, say, patch up a damaged heart, or create a synthetic knee that functions better than any artificial replacement. But because mammalian cells are so complex, this is a much more daunting task than programming bacteria. So far, Weiss and his collaborators have managed to program adult stem cells from mice to fluoresce in different colors, depending on what molecule is added to their petri dish. Though these baby steps emphasize how much is left to do, they represent impressive strides in the manipulation of biology. "Because of the power and flexibility that it offers, synthetic biology will provide many benefits to existing fields," Weiss says. "But more importantly, it will also enable an array of applications in the future that we cannot even imagine today." As the synergy between engineers and biologists grows, so do fantastic possibilities for personalized medicine, sensing and control, defense—almost any field conceivable. **LAUREN GRAVITZ**

OTHER LEADERS
in Synthetic Biology

JAMES J. COLLINS
Boston University
(Boston, MA)
Computer modeling and creation of synthetic gene networks

MICHAEL ELOWITZ
Caltech
(Pasadena, CA)
Biological computing

JAY KEASLING
University of California, Berkeley
(Berkeley, CA)
Engineering microbial metabolisms for bioremediation

TOM KNIGHT
DREW ENDY
MIT
(Cambridge, MA)
Standardizing interchangeable, interlocking microbial circuits

J. CRAIG VENTER
Institute for Biological Energy Alternatives
(Rockville, MD)
Engineering microorganisms to produce hydrogen for fuel cells

PEIDONG YANG

Nanowires

Few emerging technologies have offered as much promise as nanotechnology, touted as the means of keeping the decades-long electronics shrinkfest in full sprint and transfiguring disciplines from power production to medical diagnostics. Companies from Samsung Electronics to Wilson Sporting Goods have invested in nanotech, and nearly every major university boasts a nanotechnology initiative. Red hot, even within this R&D frenzy, are the researchers learning to make the nanoscale wires that could be key elements in many working nanodevices.

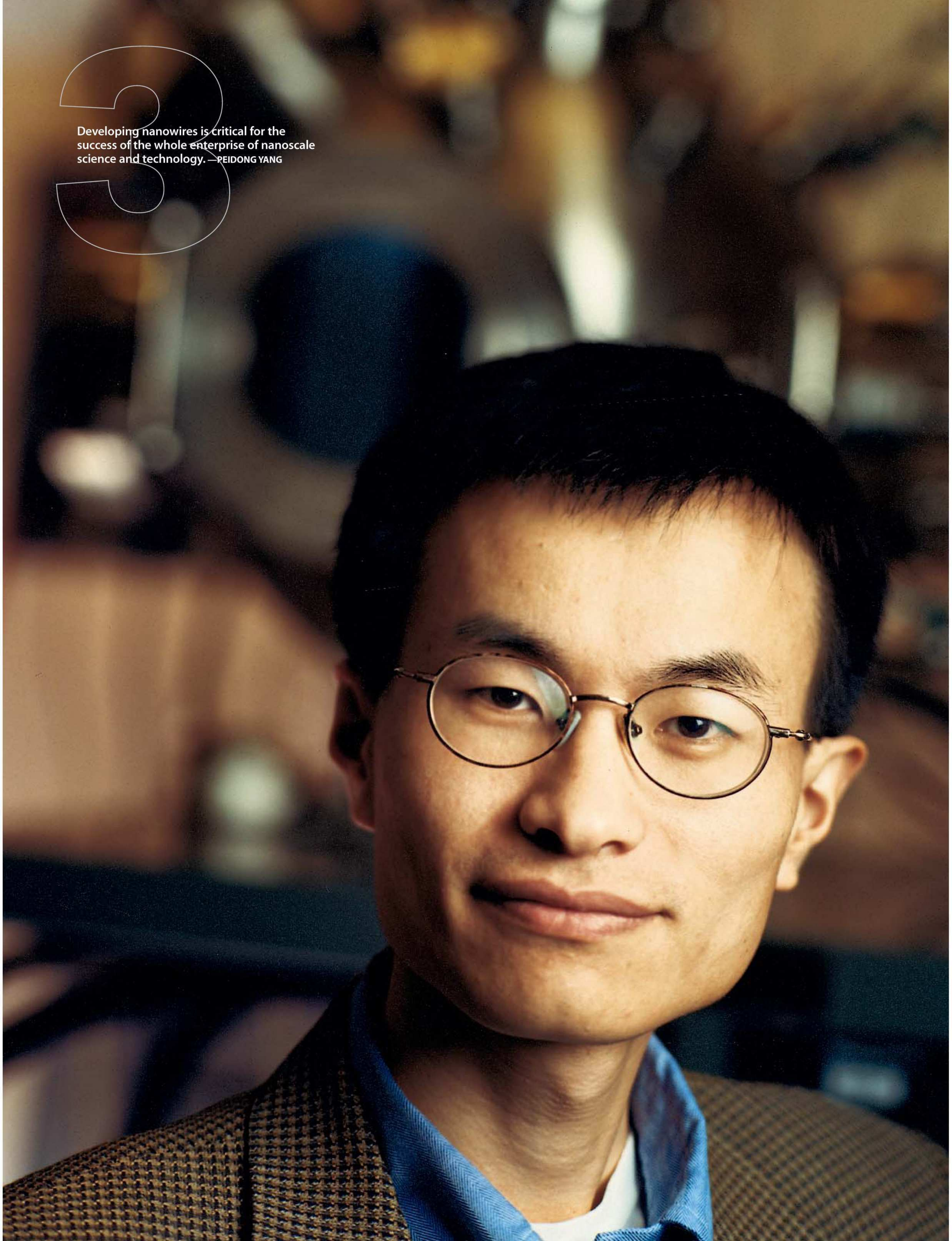
"This effort is critical for the success of the whole [enterprise of] nanoscale science and technology," says nanowire pioneer **Peidong Yang** of the University of California, Berkeley. Yang has made exceptional progress in fine-tuning the properties of nanowires. Compared to other nanostructures, "nanowires will be much more versatile, because we can achieve so many different properties just by varying the composition," says Charles Lieber, a Harvard University chemist who has also been propelling nanowire development.

As their name implies, nanowires are long, thin, and tiny—perhaps one-ten-thousandth the width of a human hair. Researchers can now manipulate the wires' diameters (from five to several hundred nanometers) and lengths (up to hundreds of micrometers). Wires have been made out of such materials as the ubiquitous semiconductor silicon, chemically sensitive tin oxide, and light-emitting semiconductors like gallium nitride.

This structural and compositional control means "we essentially can make anything we want to," says Lieber, who cofounded Palo Alto, CA-based Nanosys (to which Yang also consults) to develop nanowire-based devices. The wires can be fashioned into lasers, transistors, memory arrays, perhaps even chemical-sensing structures akin to a bloodhound's famously sensitive sniffer, notes James Ellenbogen, head of the McLean, VA-based nanosystems group at federally funded Mitre. Many of these applications require organizing nanowires into larger structures, a technical challenge that Ellenbogen credits Yang with pushing forward more than anyone.

To make the wires, Yang and his colleagues use a special chamber, inside which they melt a film of gold or another metal, forming nanometer-scale droplets. A chemical vapor, such as silicon-bearing silane, is emitted over the droplets, and its molecules decompose. In short order, those molecules supersaturate the molten nanodroplets and form a nanocrystal. As more vapor decomposes onto the metal droplet, the crystal grows upward like a tree.

DEBRA MCCLINTON



Developing nanowires is critical for the success of the whole enterprise of nanoscale science and technology. —PEIDONG YANG

Doing this simultaneously on millions of metallic drops—perhaps arranged in specific patterns—allows scientists to organize massive numbers of nanowires. Yang has already grown forests of gallium nitride and zinc oxide nanowires that emit ultraviolet light, a trait that could prove useful for "lab on a chip" devices that quickly and cheaply analyze medical, environmental, and other samples.

By introducing different vapors during the growth process, Yang has also been able to vary the wires' composition, creating complex nanowires "striped" with alternating segments of silicon and the semiconductor silicon germanium. The wires conduct heat poorly but electrons well—a combination suited for thermoelectric devices that convert heat gradients into electrical currents. "An early application might be cooling computer chips," Yang predicts. Such devices might eventually be developed into highly efficient power sources that generate electricity from cars' waste heat or the sun's heat.

Difficult tasks remain, such as making electrical connections between the minuscule wires and the other components of any system. Still, Yang estimates there are now at least 100 research groups worldwide devoting significant time to overcoming such obstacles, and commercial development efforts have already begun. Last year, Intel, which is working with Lieber, revealed that nanowires are part of its long-term chip planning. Smaller firms such as Nanosys and QuMat Technologies, a startup now renting space at Lund University in Sweden, are betting that nanowires will be essential components of the products they hope to sell one day, from sensors for drug discovery and medical diagnosis to flat-panel displays and superefficient lighting. When this catalogue of nanowired gizmos finally hits the market, Yang and his colleagues will have made no small contribution. **IVAN AMATO**

OTHER LEADERS in Nanowires

JAMES ELLENBOGEN
Mitre
(McLean, VA)
Nanosystems for computing and sensing

CHARLES LIEBER
Harvard University
(Cambridge, MA)
and Nanosys
(Palo Alto, CA)
Nanowires for computing and medical sensors

LARS SAMUELSON
Lund University and QuMat Technologies
(Lund, Sweden)
Nanowire devices for lighting, displays, and electronics

ZHONG L. WANG
Georgia Institute of Technology
(Atlanta, GA)
Nanostructures to detect molecules and viruses inside a cell

DAPHNE KOLLER

Bayesian Machine Learning

When a computer scientist publishes genetics papers, you might think it would raise colleagues' eyebrows. But **Daphne Koller**'s research using a once obscure branch of probability theory called Bayesian statistics is generating more excitement than skepticism. The Stanford University associate professor is creating programs that, while tackling questions such as how genes function, are also illuminating deeper truths about the long-standing computer science conundrum of uncertainty—learning patterns, finding causal relationships, and making predictions based on inevitably incomplete knowledge of the real world. Such methods promise to advance the fields of foreign-language translation, microchip manufacturing, and drug discovery, among others, sparking a surge of interest from Intel, Microsoft, Google, and other leading companies and universities.

How does an idea conceived by an 18th-century minister (Thomas Bayes) help modern computer science? Unlike older approaches to machine reasoning, in which each causal connection ("rain makes grass wet") had to be explicitly taught, programs based on probabilistic approaches like Bayesian math can take a large body of data ("it's raining," "the grass is wet") and deduce likely relationships, or "dependencies," on their own. That's crucial because many decisions programmers would like to automate—say, personalizing search engine results according to a user's past queries—can't be planned in advance; they require machines to weigh unforeseen combinations of evidence and make their best guesses. Says Intel research director David Tennenhouse, "These techniques are going to impact everything we do with computers—from user interfaces to sensor data processing to data mining."

Koller unleashed her own Bayesian algorithms on the problem of gene regulation—a good fit, since the rate at which each gene in a cell is translated into its corresponding protein depends on signals from a myriad of proteins encoded by other genes. New biomedical technologies are providing so much data that researchers are, paradoxically, having trouble untangling all these interactions, which is slowing the search for new drugs to fight diseases from cancer to diabetes. Koller's program combs through data on thousands of genes, testing the probability that changes in the activity of certain genes can be explained by changes in the activity of others. The program not only independently detected well-known interactions identified through years of research but also uncovered the functions of several previously mysterious regulators. "People are limited in their ability to integrate many different pieces of evidence," says Koller. "Computers have no such limitation."

Of course, Koller isn't alone in the struggle to cope with uncertainty. But according to David Heckerman, manager of the Machine Learning and Applied Statistics Group at Microsoft Research, she has uniquely extended the visual models used by Bayesian programmers—typically, graphs showing objects, their properties, and the relationships among them—so that they can represent more complex webs of dependencies. Predicting an AIDS patient's response to a medication, for example, depends on knowing how prior patients responded—but also on the par-

People are limited in their ability to integrate many different pieces of evidence. Computers are not. —DAPHNE KOLLER

DEBRA MCCLINTON

ticular strains of the virus the patients carried, which strains are drug resistant, and a multitude of other factors. Older Bayesian programs couldn't handle such multilayered relationships, but Koller found ways to "represent the added structure and reason with it and learn from it," says Heckerman.

Researchers are adapting such methods for an armada of practical applications. Among them: robots that can autonomously map hazardous, abandoned mines and programs under development at Intel that interpret test data on the quality of semiconductor wafers. In addition, several graduates of Koller's lab have joined Google, where they are using Bayesian methods to find and exploit patterns in the vast amount of interconnected data on the Web.

Programs that employ Bayesian techniques are already hitting the market: Microsoft Outlook 2003, for instance, includes Bayesian office assistants. English firm Agena has created Bayesian software that recommends TV shows to satellite and cable subscribers based on their viewing habits; Agena hopes to deploy the technology internationally. "These things sound far out," says Microsoft researcher Eric Horvitz, who, with Heckerman, is a leading proponent of probabilistic methods. "But we are creating usable tools now that you'll see in the next wave of software." **WADE ROUSH**

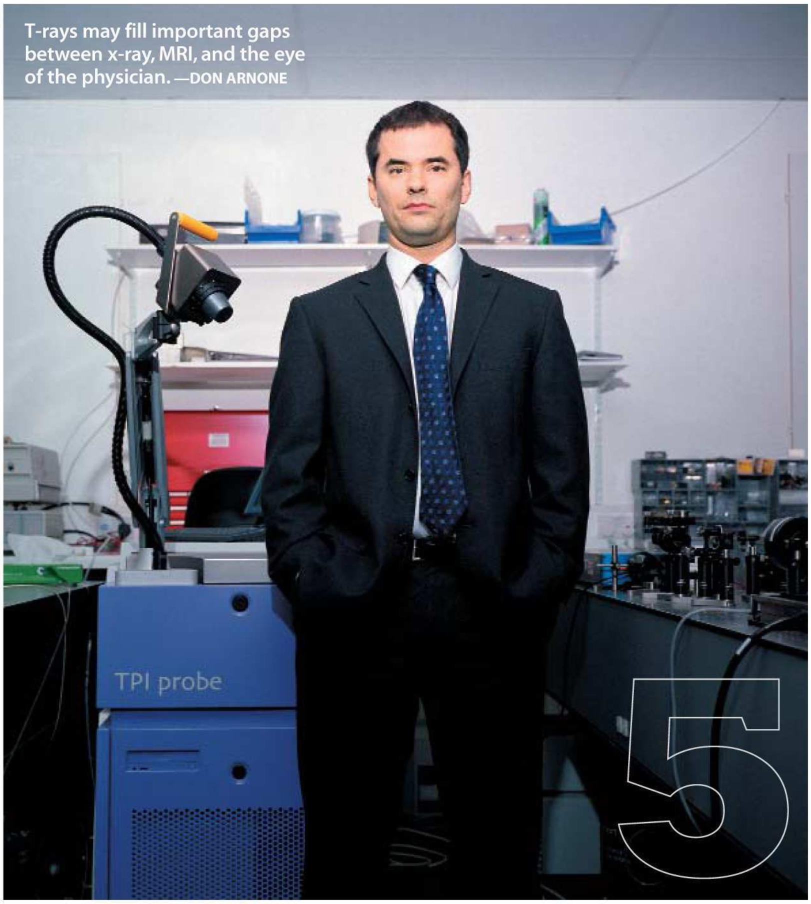
OTHER LEADERS
in Bayesian Machine Learning

GARY BRADSKI
Intel Architecture Research Laboratory (Santa Clara, CA)
Manufacturing tools; open-source Bayesian software

DAVID HECKERMAN
ERIC HORVITZ
Microsoft Research (Redmond, WA)
Spam filtering; advanced data-mining tools; intelligent office assistants

MICHAEL I. JORDAN
University of California, Berkeley (Berkeley, CA)
Graphical models; bioinformatics; information retrieval

SEBASTIAN THRUN
Stanford University (Palo Alto, CA)
Robot navigation and mapping



T-rays may fill important gaps between x-ray, MRI, and the eye of the physician. —DON ARNONE

DON ARNONE

T-Rays

With the human eye responsive to only a narrow slice of the electromagnetic spectrum, people have long sought ways to see beyond the limits of visible light. X-rays illuminate the ghostly shadows of bones, ultraviolet light makes certain chemicals shine, and near-infrared radiation provides night vision. Now researchers are working to open a new part of the spectrum: terahertz radiation, or t-rays. Able to easily penetrate many common materials without the medical risks of x-rays, t-rays promise to transform fields like airport security and medical imaging, revealing not only the shape but also the composition of hidden objects, from explosives to cancers.

In the late 1990s, **Don Arnone** and his group at Toshiba's research labs in Cambridge, England, were eyeing t-rays as an alternative to dental x-rays. The idea was that t-rays, operating in the deep-infrared region just before wavelengths stretch into microwaves, would be able to spot decay without harmful ionizing radiation. In tests, the researchers fired powerful but extremely short pulses of laser light at a semiconductor chip, producing terahertz radiation (so called because it has frequencies of trillions of waves per second). Passing through gaps or different thicknesses of material changes the rays' flight time, so by measuring how long each t-ray took to pass through an extracted tooth and reach a detector, the researchers were able to assemble a 3-D picture of the tooth.

Toshiba soon decided that the technique, while promising, didn't really fit its business. So in 2001 the company spun off a new venture, TeraView, with Arnone as CEO. Last August, TeraView started selling evaluation versions of a t-ray scanner, with major production planned to begin in a year or two. The machine looks—and works—much like a photocopier. An object sits on the imaging window, the t-ray beam passes across it, a detector measures the transmitted rays, and a screen displays the image. A separate probe arm scans objects that won't fit on the window.

Xi-Cheng Zhang, director of the Center for Terahertz Research at Rensselaer Polytechnic Institute, warns that the technology is far from mature. However, he notes, "we cannot afford not to investigate it." Indeed, several firms are already testing the TeraView scanner. Consumer electronics companies could use t-rays to check devices for manufacturing flaws. Food processors could probe the water content of sealed packages to ensure freshness. In fact, any sealed container can be probed for quality-assurance purposes. "Every factory in the world that uses a plastic or cardboard box could use one of these things, in principle," says Daniel Mittleman, a terahertz researcher at Rice University. But that's just the beginning.

Security seems another natural application. Because different chemical structures absorb them differently, t-rays could be used to identify hidden materials. TeraView is in talks with both the U.K. and U.S. governments to develop a scanner that could be used alongside metal detectors. "You can do things like look at razor blades in coat pockets or plastic explosives in shirt pockets," Arnone says. The company is building a library of spectral fingerprints of different materials.

T-ray systems might also be useful for identifying skin cancers or, with further development, breast cancers. They could show the shape of tumors and help doctors excise diseased tissue more accurately. "Because tumors tend to retain more water, they show up very brightly in terahertz images," Arnone says. "[T-rays] may fill important gaps between x-ray, MRI, and the naked eye of the physician."

Other companies are getting into the act. Japanese camera maker Nikon has developed its own t-ray scanner. Ann Arbor, MI, startup Picometrix recently sold NASA a scanner to search for gaps in space shuttles' foam insulation. And laser manufacturer Coherent in Santa Clara, CA, is one of several groups trying to develop cheaper, more compact laser sources that will

OTHER LEADERS
in Terahertz Imaging Systems

MARTYN CHAMBERLAIN
University of Leeds
(Leeds, England)
Remote sensing; medical imaging

JÉRÔME FAIST
University of Neuchâtel
(Neuchâtel, Switzerland)
New laser sources for t-ray production

QING HU
MIT
(Cambridge, MA)
New laser sources for t-ray production

DANIEL MITTLEMAN
Rice University
(Houston, TX)
New t-ray imaging techniques

XI-CHENG ZHANG
Rensselaer Polytechnic Institute
(Troy, NY)
Imaging biomolecules and semiconductors

JONATHAN WORTH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*Source: KPMG 2002 – G7 (excludes Russia) 12-industry average.
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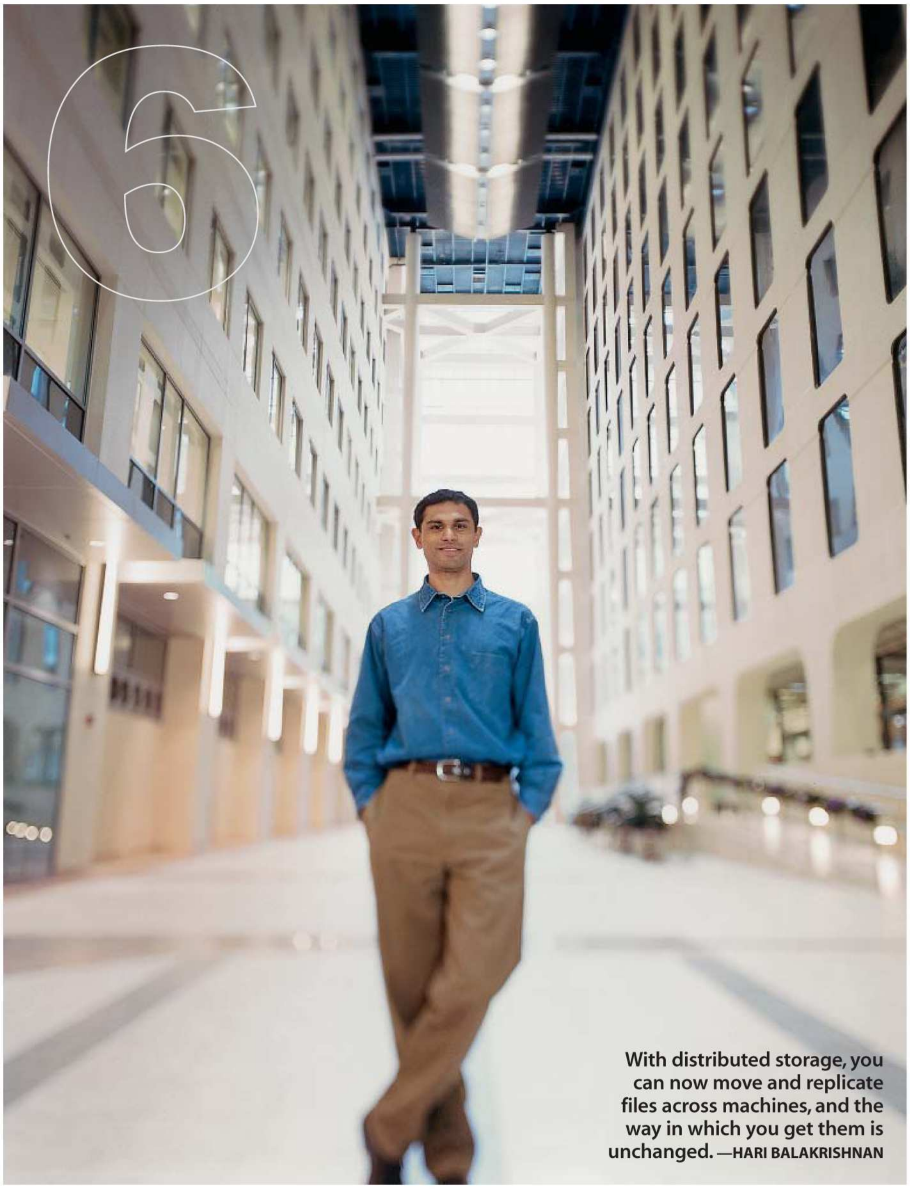


With distributed storage, you can now move and replicate files across machines, and the way in which you get them is unchanged. —HARI BALAKRISHNAN

make t-ray systems easier to build. In the part of the spectrum between the domains of cell phones and lasers, t-rays could shed light on mysteries hidden from even today's most technologically enhanced eyes. **NEIL SAVAGE**

6

HARI BALAKRISHNAN

Distributed Storage

Whether it's organizing documents, spreadsheets, music, photos, and videos or maintaining regular backup files in case of theft or a crash, taking care of data is one of the biggest hassles facing any computer user. Wouldn't it be better to store data in the nooks and crannies of the Internet, a few keystrokes away from any computer, anywhere? A budding technology known as distributed storage could do just that, transforming data storage for individuals and companies by making digital files easier to maintain and access while eliminating the threat of catastrophes that obliterate information, from blackouts to hard-drive failures.

Hari Balakrishnan is pursuing this dream, working to free important data from dependency on specific computers or systems. Music-sharing services such as KaZaA, which let people download and trade songs from Internet-connected PCs, are basic distributed-storage systems. But Balakrishnan, an MIT computer scientist, is part of a coalition of programmers who want to extend the concept to all types of data. The beauty of such a system, he says, is that it would provide all-purpose protection and convenience without being complicated to use. "You can now move [files] across machines," he says. "You can replicate them, remove them, and the way in which [you] get them is unchanged." With inability to access data sometimes costing companies millions in revenue per hour of downtime, according to Stamford, CT-based Meta Group, a distributed-storage system could dramatically enhance productivity.

Balakrishnan's work centers on "distributed hash tables," an update on a venerable computer-science concept. Around since the 1950s, hash tables provide a quick way to organize data: a simple mathematical operation assigns each file its own row in a table; the row stores the file's location. Such tables are now ubiquitous, forming an essential part of most software.

In the distributed-storage scheme pursued by Balakrishnan and his colleagues, files are scattered around the Internet, as are the hash tables listing their locations. Each table points to other tables, so while the first hash table searched may not list the file you want, it will point to other tables that will eventually—but still within milliseconds—reveal the file's location. The trick is to devise efficient ways to route data through the network—and to keep the tables up to date. Get it right and distributed hash tables could turn the Internet into a series of automatically organized, easily searchable filing cabinets. Balakrishnan says, "I view distributed hash tables as the coming future" of networked storage.

Balakrishnan's work is part of IRIS, the Infrastructure for Resilient Internet Systems project, a collaboration among researchers at MIT, the University of California, Berkeley, the International Computer Science Institute in Berkeley, CA, New York University, and Rice University. The effort, funded by the National Science Foundation, has no director (Balakrishnan always uses "we" and "us" when describing the work). Its research includes several distributed-storage projects, including OceanStore, which seeks to prove the basic concepts of distributed-storage networks *(see "The Internet Reborn," TR October 2003)*. Another MIT researcher, Frans Kaashoek, is developing a prototype that automatically backs up data by routinely taking file system "snapshots" and distributing them around the Internet.

ASIA KEPKA

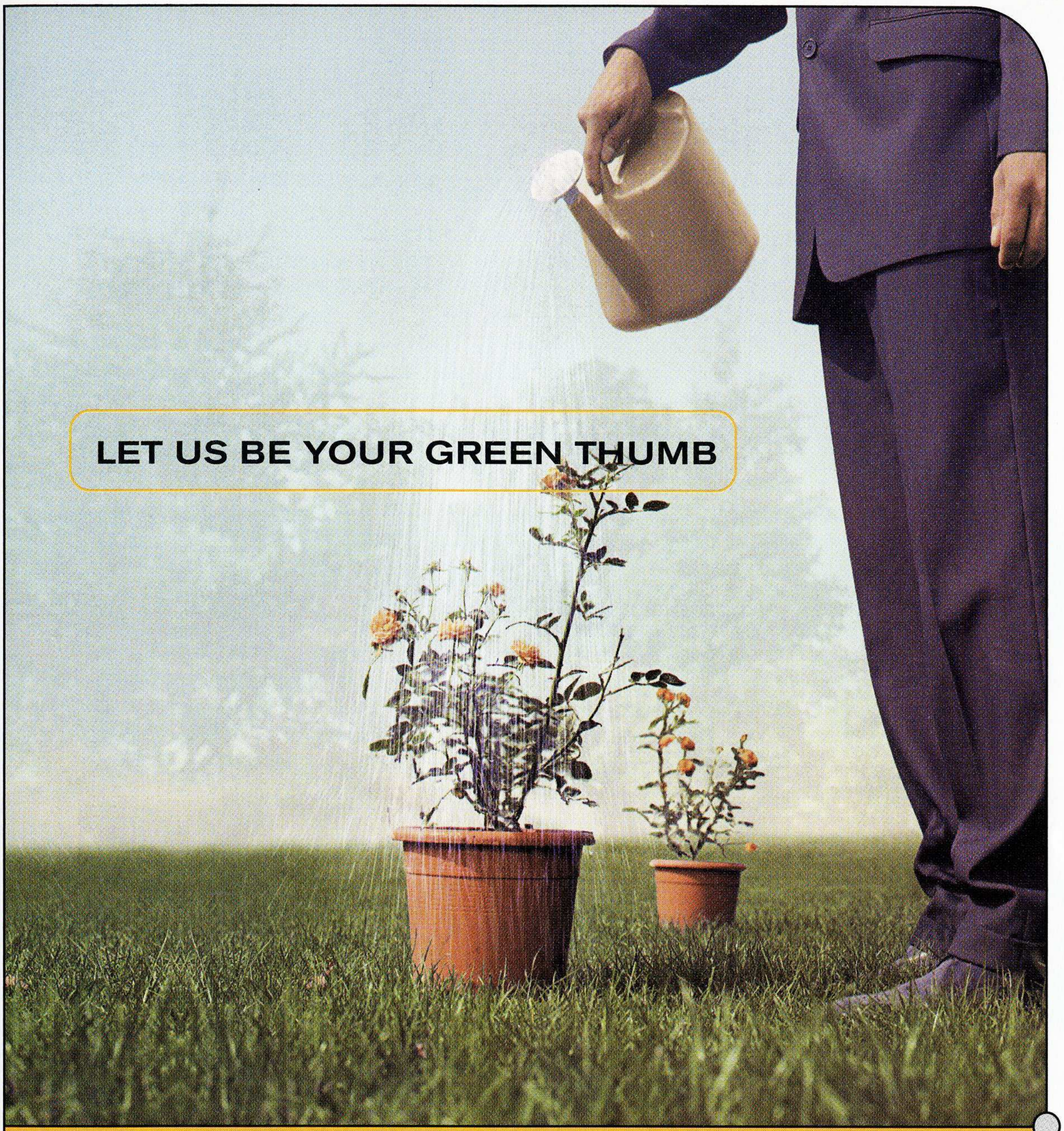
OTHER LEADERS
in Distributed Storage

: IAN CLARKE
Freenet
(Open-source project)
Anonymous content publishing and distribution

: JOHN KUBIATOWICZ
University of California, Berkeley
(Berkeley, CA)
Secure distributed storage over the Internet

: TOM LEIGHTON
Akamai
(Cambridge, MA)
Internet content distribution

: MICHAEL LYNCH
Autonomy
(Cambridge, England)
Distributed corporate databases



CULTIVATING GROWTH

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RNAi worked the first time we did the experiment. —THOMAS TUSCHL

It will be at least five years before the impact of IRIS becomes clear. Balakrishnan says the group still has to figure out how to track file updates across multiple storage sites and whether distributed hash tables should be built into the Internet foundation or incorporated into individual applications—as well as the answers to basic security questions.

But it's the fundamental power of the technology that excites many computer scientists. "What's striking about it is its huge variety of applications," says Sylvia Ratnasamy, a researcher at Intel's laboratory at Berkeley who is exploring ways that distributed storage might change the basic operation of the Internet. "Not very many technologies have that broad potential."

Stay tuned. Turning the Internet into a filing cabinet may be just step one. **MICHAEL FITZGERALD**

THOMAS TUSCHL

RNAi Therapy

From heart disease to hepatitis, cancer to AIDS, a host of modern ailments are triggered by our own errant genes—or by those of invading organisms. So if a simple technique could be found for turning off specific genes at will, these diseases could—in theory—be arrested or cured. Biochemist **Thomas Tuschl** may have found just such an off switch in humans: RNA interference (RNAi). While working at Germany's Max Planck Institute for Biophysical Chemistry, Tuschl discovered that tiny double-stranded molecules of RNA designed to target a certain gene can, when introduced into human cells, specifically block that gene's effects.

Tuschl, now at Rockefeller University in New York City, first presented his findings at a meeting in Tokyo in May 2001. His audience was filled with doubters who remembered other much hyped RNA techniques that ultimately didn't work very well. "They were very skeptical and very critical," recalls Tuschl. What the skeptics didn't realize was that RNAi is much more potent and reliable than earlier methods. "It worked the first time we did the experiment," Tuschl recalls. Within a year, the doubts had vanished, and now the technique has universal acceptance—spawning research at every major drug company and university and likely putting Tuschl on the short list for a Nobel Prize.

The implications of RNAi are breathtaking, because living organisms are largely defined by the exquisitely orchestrated turning on and off of genes. For example, a cut on a finger activates blood-clotting genes, and clot formation in turn shuts them down. "Just about anything is possible with this," says John Rossi, a molecular geneticist at the City of Hope National Medical Center in Duarte, CA, who advises Australian RNAi startup Benitec. "If you knock out gene expression, you could have big impacts on any disease, any infectious problem." Pharmaceutical companies are already using RNAi to discover drug targets, by simply blocking the activity of human genes, one by one, to see what happens. If, for instance, a cancer cell dies when a particular gene is shut down, researchers can hunt for drugs that target that gene and the proteins it encodes. Screening the whole human genome this way "is not complicated," Tuschl points out.

Now drug companies, along with biotech startups and academic researchers, are seeking to use RNAi to treat disease directly. In fact, Tuschl cofounded one such startup, Alnylam Pharmaceuticals in Cambridge, MA *(see "The RNA Cure?"* TR *November 2003)*, which hopes to create RNAi drugs to treat cancer, AIDS, and other diseases. For example, silencing a key gene in the HIV virus could stop it from causing AIDS; knocking out the mutated gene that causes Huntington's could halt the progression of the disease; and turning off cancer genes could shrink tumors. "It's going to be a very, very powerful approach," says Rossi.

The interference process works by preventing the gene from being translated into the protein it encodes. (Proteins do most of the real work of biology.) Normally, a gene is transcribed into an intermediate "messenger RNA" molecule, which is used as a template for assembling a protein. When a small interfering RNA molecule is introduced, it binds to the messenger, which cellular scissors then slice up and destroy.

The biggest hurdle to transforming RNAi from laboratory aide to medicine is delivering the RNA to a patient's cells, which are harder to access than the individual cells used in lab experiments. "That's the major limitation right now," says Rossi, who nevertheless predicts that RNAi-based therapies could be on the market "within maybe three or four years." Tuschl is more cautious. He thinks the technique's first applications—say, local delivery to the eye to treat a viral infection—may indeed come that soon. But he says it could take a decade or longer to develop a system that effectively delivers RNAi drugs to larger organs or the whole body.

Tuschl's lab is one of many now teasing out the precise molecular mechanisms responsible for RNA interference's remarkable potency, hoping to help realize the payoffs of RNA drugs sooner rather than later. Presuming the tiny RNA molecules can fulfill the promise of their fast start, traditional molecular biology will be turned on its head. **KEN GARBER**

OTHER LEADERS
in RNAi Therapy

REUVEN AGAMI
Netherlands Cancer Institute (Amsterdam, the Netherlands)
Cancer

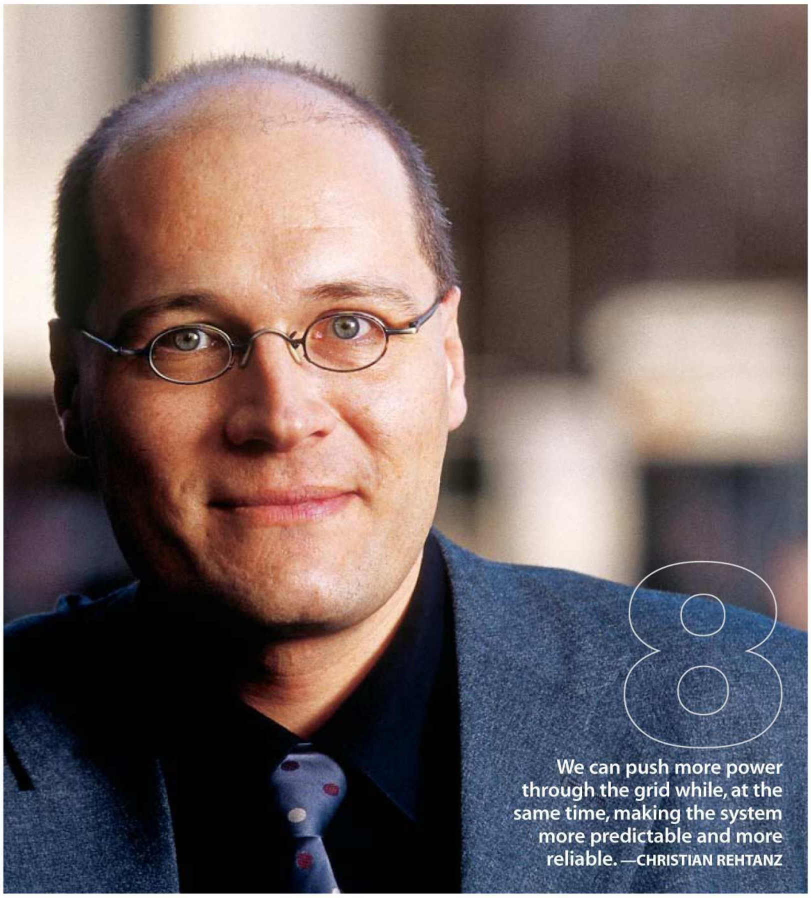
BEVERLY DAVIDSON
University of Iowa (Iowa City, IA)
Huntington's disease

MICHAEL GRAHAM
Benitec (Queensland, Australia)
Cancer, AIDS

MARK KAY
Stanford University (Palo Alto, CA)
Hepatitis B and C

JUDY LIEBERMAN
Harvard University (Cambridge, MA)
AIDS, hepatitis, cancer

DENNIS KLEIMAN



WILLY SPILLER/GETTY

OTHER LEADERS
in Power Grid Control

: JOHN HAUER
Pacific Northwest National Laboratory (Richland, WA)
Monitoring and analyzing U.S. power flows

: INNOCENT KAMWA
Hydro-Québec Research Institute (Varennes, Québec)
Securing power flows in Canada

: CARSON TAYLOR
Bonneville Power Administration (Portland, OR)
Wide-area measurement systems to stabilize west-coast power lines

: VIJAY VITTAL
Iowa State University (Ames, IA)
Simulation of large-scale power systems

CHRISTIAN REHTANZ

Power Grid Control

Power grids carry the seeds of their own destruction: massive flows of electricity that can race out of control in just seconds, threatening to melt the very lines that carry them. Built in the days before quick-reacting microprocessors and fiber optics, these networks were never designed to detect and squelch systemwide disturbances. Instead, each transmission line and power plant must fend for itself, shutting down when power flows spike or sag. The shortcomings of this system are all too familiar to the 50 million North Americans from Michigan to Ontario whose lights went out last August: as individual components sense trouble and shut down, the remaining power flows become even more disturbed, and neighboring lines and plants fall like multimillion-dollar dominoes. Often-needless shutdowns result, costing billions, and the problem is only expected to get worse as expanding economies push more power onto grids.

Christian Rehtanz thinks the time has come for modern control technology to take back the grid. Rehtanz, group assistant vice president for power systems technology with Zürich, Switzerland-based engineering giant ABB, is one of a growing number of researchers seeking to build new smarts into grid control rooms. These engineers are developing hardware and software to track electric flows across continent-wide grids several times a second, identify disturbances, and take immediate action. While such "wide area" control systems remain largely theoretical, Rehtanz and his ABB colleagues have fashioned one that is ready for installation today. If their design works as advertised, it will make power outages 100 times less likely, protecting grids against everything from consumption-inducing heat waves to terrorism. "We can push more power through the grid while, at the same time, making the system more predictable and more reliable," says Rehtanz.

Real-time control systems are a natural outgrowth of a detection system pioneered in the 1990s by the U.S.-government-operated Bonneville Power Administration, which controls grids in the Pacific Northwest. In this system, measurements from sensors hundreds to thousands of kilometers apart are coded with Global Positioning System time stamps, enabling a central computer to synchronize data and provide an accurate snapshot of the entire grid 30 times per second—fast enough to glimpse the tiny power spikes, sags, and oscillations that mark the first signs of instability. An earlier version of Bonneville's system helped explain the dynamics of the 1996 blackout that crippled 11 western U.S. states, Alberta, British Columbia, and Baja California; western utilities subsequently rejiggered their operations and have thus far avoided a repeat. "I know the people back east sure wish they had one right now," says Carson Taylor, Bonneville's principal engineer for transmission and an architect of its wide-area system.

But Rehtanz is eager to take the next step, transforming these investigative tools into real-time controls that detect and squelch impending blackouts. The technical challenge: designing a system that can respond quickly enough. "You have half a minute, a minute, maybe two minutes to take action," says Rehtanz. That requires spartan calculations that can crunch the synchronized sensor data, generate a model of the system to detect impending disaster, and select an appropriate response, such as turning on an extra power plant. Control algorithms designed by Rehtanz and his colleagues employ a highly simplified model of how a grid works, but one that they believe is nevertheless capable of instantly identifying serious problems brewing—and on a standard desktop computer. ABB engineers are now studying how such algorithms could protect a critical power corridor linking Switzerland and Italy that failed last September, blacking out most of Italy.

Many utilities are already implementing elements of real-time grid control—for example, installing digital network controllers that can literally push power from one line to another or suppress local spikes and sags *(see "Power Gridlock,"* TR *July/August 2001)*. Tied into a wide-area

control scheme, these network controllers could perform more intelligently. Still, it may be years before a utility takes the plunge and fully commits to Rehtanz's algorithms. It's not just that utilities are conservative about tinkering with untried technologies; cash for transmission upgrades is thin in today's deregulated markets, where it's unclear which market players—power producers, transmission operators, or government regulators—should pay for reliability. What is clear, however, is that the evolution toward real-time, wide-area sensing and control has begun.

PETER FAIRLEY

JOHN ROGERS

Microfluidic Optical Fibers

The blazing-fast Internet access of the future—imagine downloading movies in seconds—might just depend on a little plumbing in the network. Tiny droplets of fluid inside fiber-optic channels could improve the flow of data-carrying photons, speeding transmission and improving reliability. Realizing this radical idea is the goal of University of Illinois physicist **John Rogers**, whose prototype devices, called microfluidic optical fibers, may be the key to superfast delivery of everything from e-mail to Web-based computer programs, once "bandwidth" again becomes the mantra.

Rogers began exploring fluid-filled fibers more than two years ago as a researcher at Lucent Technologies' Bell Labs. While the optical fibers that carry today's phone and data transmissions consist of glass tubing that is flexible but solid, Rogers employs fibers bored through with microscopic channels, ranging from one to 300 micrometers in diameter, depending on their use. While Rogers didn't invent the fibers, he and his team showed that pumping tiny amounts of various fluids into them—and then controlling the expansion, contraction, and movement of these liquid "plugs"—causes the optical properties of the fibers to change. Structures such as tiny heating coils printed directly on the fiber precisely control the size, shape, and position of the plugs. Modifying the plugs' properties enables them to perform critical functions, such as correcting error-causing distortions and directing data flows more efficiently, thus boosting bandwidth far more cheaply than is possible today.

Today, these tune-up jobs are partly done by gadgets that convert light signals into electrons and then back into photons. This "removal of light" invariably causes distortions and losses. Rogers's idea is to do these jobs more directly by replacing today's gadgets with sections of fluid-filled optical fibers strategically placed in the existing network. Making sections of the fiber itself tunable could eliminate some of these "light-removing" components, Rogers says. "Anytime you can avoid the need to remove light, there is a big cost advantage, reliability advantage, and increase in capacity."

Other approaches to making fibers that actively tune light—as opposed to serving as passive pipes—are also under development. But with the telecom sector still in crash mode, leaving thousands of kilometers of underground fiber-optic cables unused, nobody expects a rapid embrace of new optical communications technologies. "These kinds of things are needed when you get to the next-generation optical networks," notes Dan Nolan, a physicist at Corning, a leading maker of optical fiber. "Right now you don't really need them, because the next generation has been put off."

Few, though, question that a push to a much faster Internet will eventually return. And when it does, Nolan says, devices like Rogers's could come into play. "I consider it very important research," Nolan adds. Though the timing for commercialization is uncertain, the fibers have already moved beyond lab demonstrations; prototype devices are being tested at both Lucent and its spinoff company OFS, a Norcross, GA-based optical-fiber manufacturer.

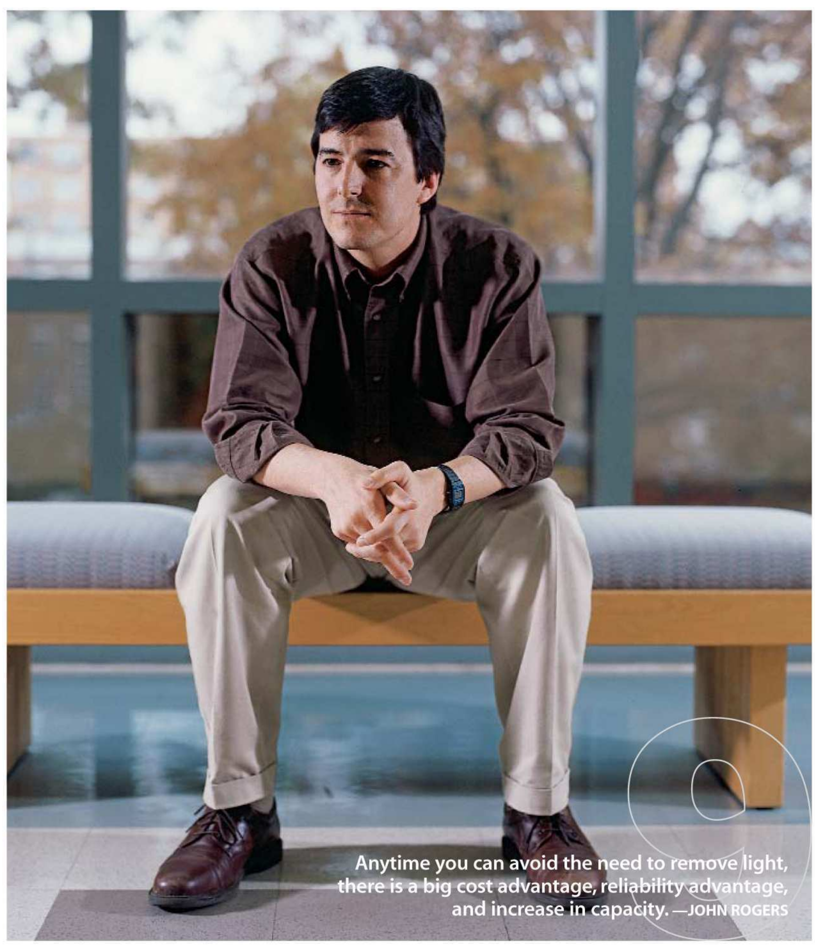
OTHER LEADERS
in Advanced Optical Fibers

:YOEL FINK
MIT
(Cambridge, MA)
Tunable polymer fibers

:TIMOFEI KROUPENKINE
Lucent Technologies' Bell Labs
(Murray Hill, NJ)
Liquid-crystal-based optical tuning

:STERLING MCBRIDE
:DENNIS PRATHER
Sarnoff
(Princeton, NJ);
University of Delaware
(Newark, DE)
Tunable lenses employing microfluidics

:DAN NOLAN
Corning Research
(Corning, NY)
Optical pulses to tune signals inside fibers



Anytime you can avoid the need to remove light, there is a big cost advantage, reliability advantage, and increase in capacity. —JOHN ROGERS

CHRIS LAKE

Still, the idea of adding a plumbing system to optical networks is jarring to some researchers. "Success will ultimately depend on how well you can put in the solution without disrupting the ends of the fiber," says Axel Scherer, a physicist at Caltech. "The question is, how do you do that in an easy and inexpensive way." MIT physicist John Joannopoulos holds similar reservations. But if the fluidics system works, Joannopoulos says, "it gives you extra control. Once you have that, then you can make devices out of these fibers, not just use them to transport something."

The marriage of optics and tiny flows of fluid also holds promise for other applications. One possibility Rogers is investigating: a tool that could use light to detect substances like disease-indicating proteins in blood, useful for medical diagnosis or drug discovery. Even if it doesn't speed your downloads, Rogers's plumbing might still improve doctors' checkups. **DAVID TALBOT**

OTHER LEADERS
in Personal Genome Analysis

: RICHARD BEGLEY
454 Life Sciences
(Branford, CT)
Simple, high-speed, cheap DNA sequencing using microfluidic technology

: DANIEL BRANTON
Harvard University
(Cambridge, MA)
Fast, accurate DNA sequencing using nanopores

: EUGENE CHAN
U.S. Genomics
(Woburn, MA)
Low-cost, fast optical DNA sequencing

: GEORGE CHURCH
Harvard University
(Cambridge, MA)
DNA sequencing using polymerase-colony technology

DAVID COX

Personal Genomics

Three billion. That's the approximate number of DNA "letters" in each person's genome. The Human Genome Project managed a complete, letter-by-letter sequence of a model human—a boon for research. But examining the specific genetic material of each patient in a doctor's office by wading through those three billion letters just isn't practical. So to achieve the dream of personalized medicine—a future in which a simple blood test will determine the best course of treatment based on a patient's genes—many scientists are taking a shortcut: focusing on only the differences between people's genomes.

David Cox, chief scientific officer of Perlegen Sciences in Mountain View, CA, is turning that strategy into a practical tool that will enable doctors and drug researchers to quickly determine whether a patient's genetic makeup results in greater vulnerability to a particular disease, or makes him or her a suitable candidate for a specific drug. Such tests could eventually revolutionize the treatment of cancer, Alzheimer's, asthma—almost any disease imaginable. And Cox, working with some of the world's leading pharmaceutical companies, has gotten an aggressive head start in making it happen.

Genetic tests can already tell who carries genes for certain rare diseases like Huntington's, and who will experience the toxic side effects of a few particular drugs, but each of these tests examines only one or two genes. Most common diseases and drug reactions, however, involve several widely scattered genes, so researchers want to find ways to analyze an individual's whole genome. Since most genetic differences between individuals are attributable to single-letter variations called single-nucleotide polymorphisms, or SNPs, Cox believes that identifying genomewide patterns of these variants that correspond to particular diagnoses or drug responses is the quickest, most cost-effective way to make patients' genetic information useful. "I would like to know whether genetics is going to be practical while I'm still alive," says Cox.

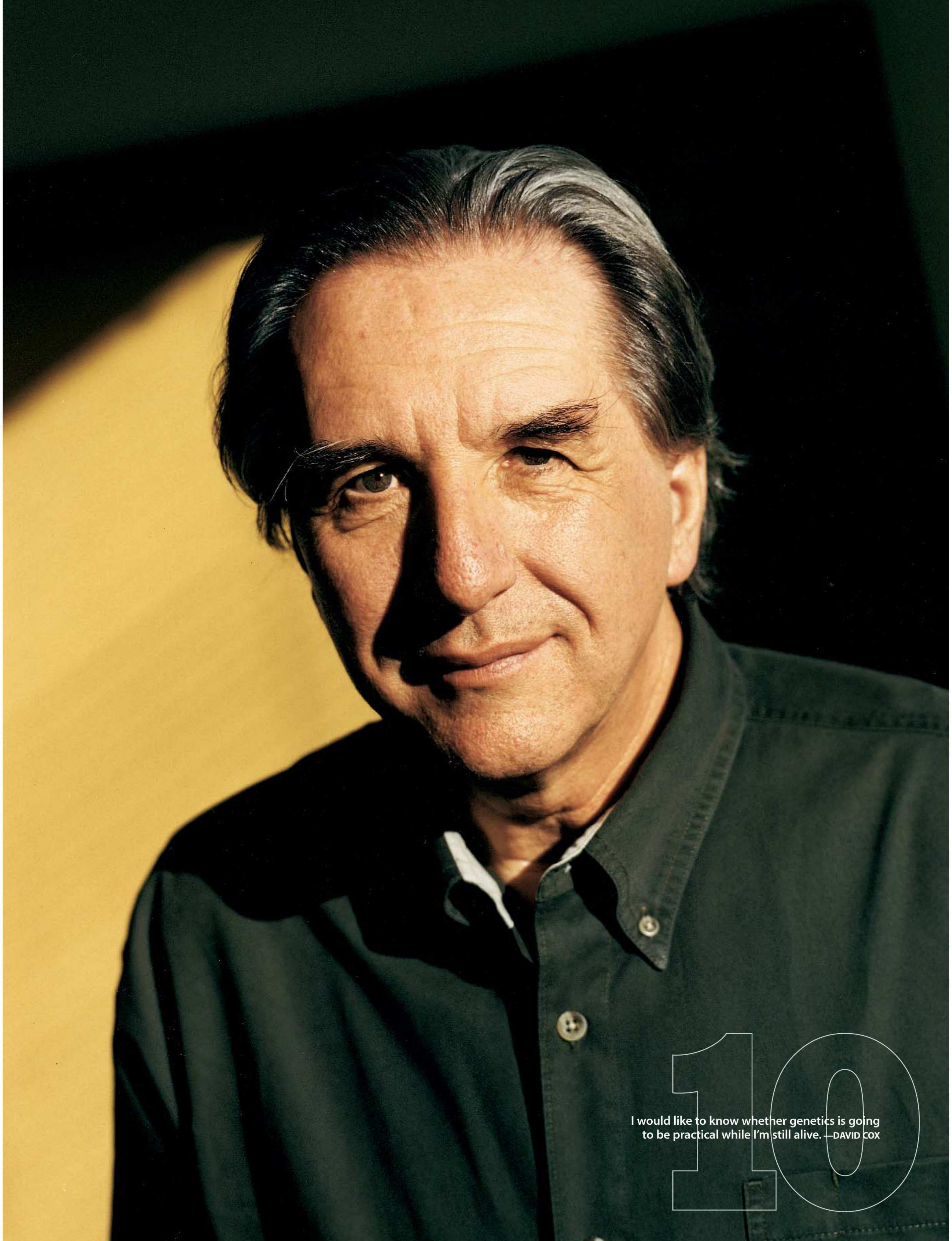
To help answer that question, in 2000 Cox left his position as codirector of the Stanford University Genome Center to cofound Perlegen, which has moved vigorously to bring SNP analysis to the clinic. The company has developed special DNA wafers—small pieces of glass to which billions of very short DNA chains are attached—that can be used to quickly and cheaply profile the millions of single-letter variants in a patient's genome. Perlegen researchers first created a detailed map of 1.7 million of the most common SNPs. Based on this map, they then designed a wafer that can detect which version of each one of these variants a specific patient has.

Now, in partnership with major pharmaceutical makers, the company is comparing genetic patterns found in hundreds of people with, for example, diabetes to those of people without it. With Pfizer, Perlegen is examining genetic contributions to heart disease; for Eli Lilly, Bristol-Myers Squibb, and GlaxoSmithKline, Perlegen researchers are hunting for SNP patterns that correlate to particularly adverse or favorable reactions to different drugs. The next step is to use this information to design a simple test that discerns telltale SNP patterns. With such a test, doctors could screen patients to identify the best drug regimen for each.

Some biologists argue that a truly accurate picture of an individual's genetics requires decoding his or her entire genome, down to every last DNA letter; but for now that is a daunting technical challenge that remains prohibitively expensive. Cox counters that SNP analysis is the quickest way to practically bring genetics and medicine together, and many geneticists share his vision of ultimately analyzing SNPs right in a doctor's office. "I think this will become a routine thing in the future," says George Weinstock, codirector of the Human Genome Sequencing Center at the Baylor College of Medicine in Houston, TX. And, adds Weinstock, "Perlegen is one of the leaders in the field."

Within a few years, genetic screening to predict a patient's drug response may become commonplace. To make that happen, it will take tools like the ones Cox and his coworkers at Perlegen are already beginning to employ. **CORIE LOK** TR

DEBRA MCCLINTON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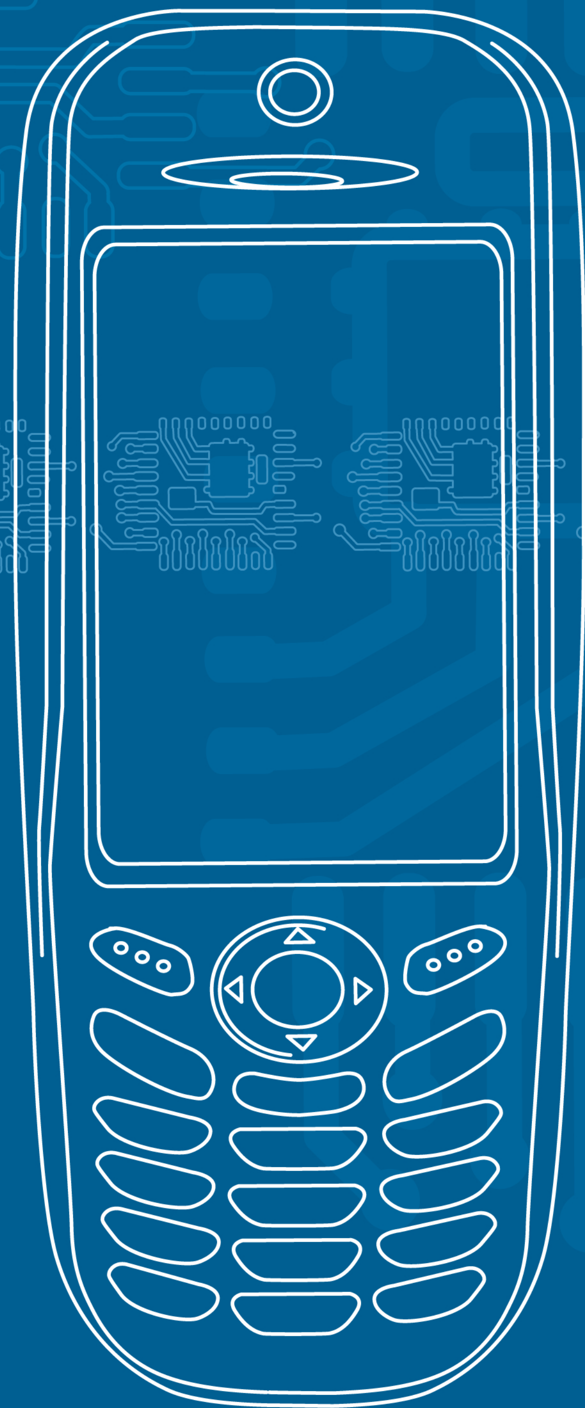
I would like to know whether genetics is going to be practical while I'm still alive. —DAVID COX

GADGETS IN THE SUPERCHIP AGE

BY DAVID H. FREEDMAN

ILLUSTRATIONS BY ULLA PUGGAARD

SEMICONDUCTOR MAKERS WILL SOON BE ABLE TO CRAM A BILLION TRANSISTORS ONTO A SINGLE MICROCHIP. HERE'S WHAT ALL THAT NEW COMPUTING POWER WILL DO FOR YOU.



FASTER PHONES

Mobile phones powered by tomorrow's microchips will communicate at higher frequencies—which means much greater data transfer speeds. Expect features like videoconferencing and graphically rich multiplayer games.

IN A LAB at Philips Electronics in the Netherlands, researchers are stalking the solution to one of the great problems of modern life: having to hunt through hundreds of television channels for something you'd like to watch. The lab's answer is a TV that recognizes you when you walk into the room, knows you like occult thrillers, finds one it recorded at three in the morning, and puts it up on the screen. Alongside will be smaller images of a British news report on the company you just invested in, the Web page carrying the eBay auction you bid in, and the high-resolution video scene you recorded on your cell phone earlier in the day. Ready to switch channels? Just speak up and tell the TV what you want.

Perhaps the best thing about this talented device is that you'll be able to buy it in about seven years for about what you'd pay for a dumb television today. Philips has already demonstrated these sorts of capabilities in its lab and recently rolled out a semi-intelligent prototype. "We can already produce a mostly digital television that allows you to add functions through software and that will cost in the ballpark of a conventional analog set," says Theo Claasen, chief technology officer for the company's semiconductor group.

We've come to take for granted that the electronics industry keeps hurling new and improved products at us, and it's a solid bet that this won't slow down in the near future. Electronic products are largely defined by the microprocessors inside them, and the power and speed of these chips continue to climb exponentially. The amazing resiliency of Moore's Law—Intel cofounder Gordon Moore's prediction nearly 40 years ago that the number of transistors on a chip would double every year—means that chips have gone from having a few thousand transistors three decades ago to over 100 million today, while the price per transistor has dropped from $1 to a millionth of a cent. And since transistor density roughly translates to computing and communications speed, you can thank Moore's Law for innovations like online shopping, in-car navigation systems, and cheap cell phones. "Transistors are free," says Krishnamurthy Soumyanath, director of communications-circuits research at Intel. "We can solve problems by throwing more transistors at them."

Despite skeptics' perennial warnings that Moore's Law will peter out, the industry is set to hew to it for at least the next three generations of microprocessors, expected to come out over the next six years. Right now the smallest standard features of the fastest silicon transistors are 90 nanometers wide. Before the end of 2005, manufacturers expect to make 65-nanometer transistors. And blueprints for reducing that to 45 nanometers by 2007 are in the works.

Miniaturization means that more transistors can be squeezed onto a chip. This makes microprocessors faster, in part because electrons have less distance to travel between transistors. It also makes memory chips more capacious. Today, the fastest consumer microprocessors have about 180 million transistors and operate at a speed of about three gigahertz—or roughly speaking, three billion simple operations per second—while the adjacent random-access memory chips hold two gigabytes of data or more. By 2007, processors will pack more than a billion transistors, hit speeds approaching 10 gigahertz, and be backed up by several gigabytes of RAM. With that kind of power and memory, PCs will be able to transport you to ultrarealistic online virtual worlds, hold up their end of a conversation (on certain topics, anyway), and quickly search through hours of your vacation videos for that bit where Uncle Arnold capsizes his canoe.

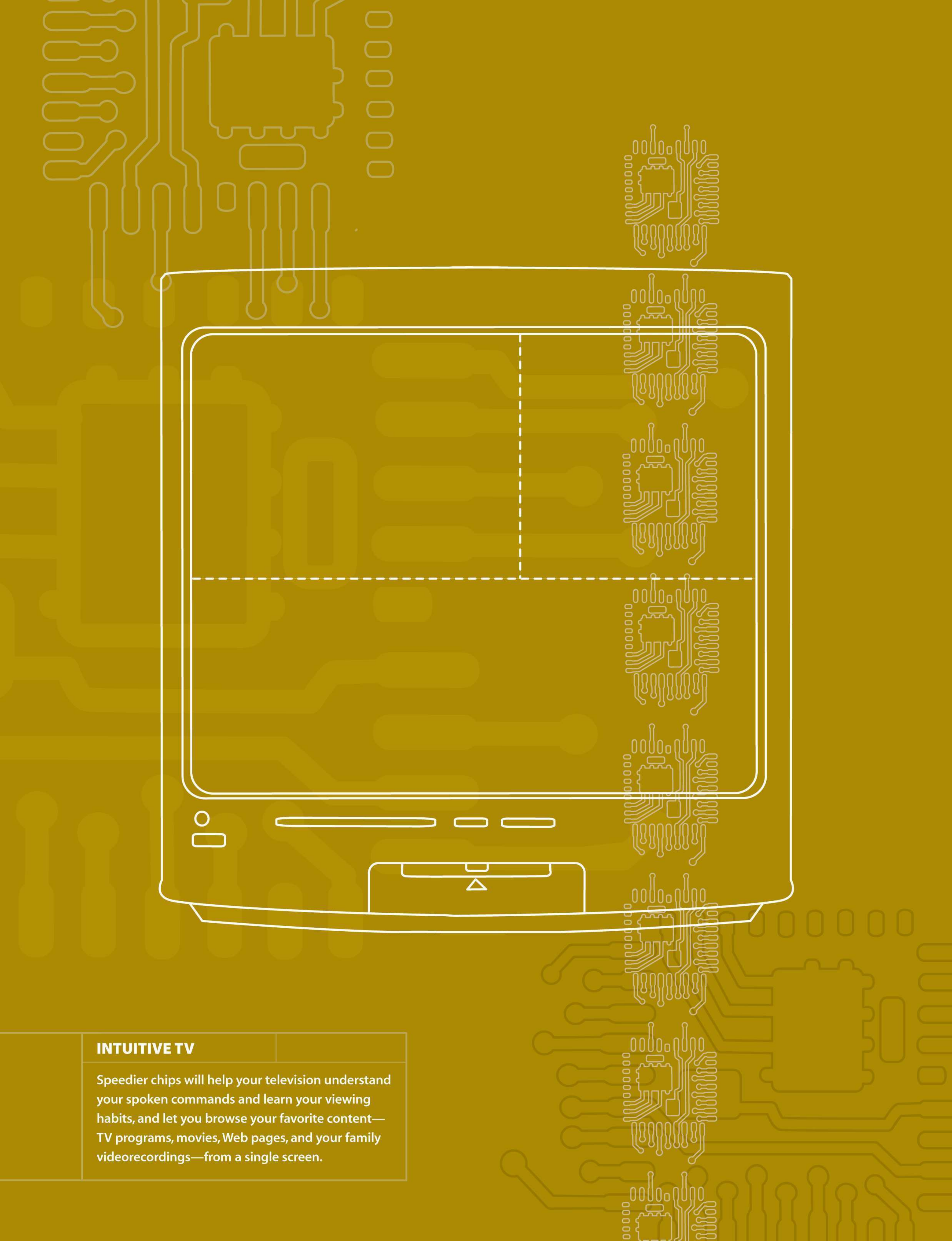
Predicting what other sorts of gadgets will result from this explosion in computing power is, of course, the $64,000—make that the $64 billion—question. For all his prescience about chips, Gordon Moore himself failed to foresee the PC or the Internet, never mind the personal digital assistant or smart cell phone. Home videophones and pen-based computers, on the other hand, have managed to stay off consumers' radar screens despite decades of hype. "If ten years ago someone told you about the World Wide Web, MP3 players, and video cameras that fit in the palm of your hand, you wouldn't have believed them," says Jeffrey Bokor, a professor in the Department of Electrical Engineering and Computer Science at the University of California, Berkeley. "What we're going to see over the coming years will be equally hard to imagine."

MOVIES ON YOUR PHONE

But plenty of experts are willing to take a stab at it. Near the top of everyone's list is the cell phone, which appears to be due for a serious makeover. For starters, says Peter Kastner, chief researcher at the Aberdeen Group, a market research firm in Boston, cell phones will pack in the electronics needed to communicate via a number of different frequencies and data-encoding schemes, so that they can constantly hunt for the channels that will give them the best data transfer rates at the lowest costs.

That means these new phones will receive data 20 or more times faster than today's mobile phones, without sending service bills through the roof. To handle these data transfer speeds, the phones will operate at frequencies in the two-gigahertz range and above, well beyond the frequency range of most cell

TVs WILL BECOME SO DEPENDENT ON COMPUTING POWER THAT CONSUMERS WILL SOON BE SHOPPING FOR THEM THE WAY THEY NOW SELECT PCs: ACCORDING TO PROCESSING SPEED, MEMORY SIZE, AND COMMUNICATIONS ABILITY.



INTUITIVE TV

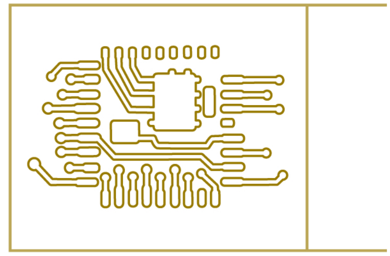
Speedier chips will help your television understand your spoken commands and learn your viewing habits, and let you browse your favorite content—TV programs, movies, Web pages, and your family videorecordings—from a single screen.

phones today. That hasn't been cost-effective until recently because the analog circuits that process traditional audio and visual signals enlist specialized transistor designs and materials. Analog circuits are also sensitive to the electronic "noise" from digital circuits, meaning they're usually stuck on separate chips—a costly and inefficient arrangement that limits devices' ability to handle ultrafast signals. But now, thanks to the performance boost that comes from more densely packed transistors, digital circuits are becoming quick enough to mimic many of the functions of analog circuits, including dealing with fast-changing, high-bandwidth radio signals. "We can take an analog radio signal right off an antenna and quickly move it into digital logic," says Dennis Buss, vice president of silicon-technology development at Texas Instruments, which is already rolling out integrated, single-chip wireless devices based on the new techniques.

With their near-broadband connections, these new phones will enable fast, high-resolution Web surfing, and even passable real-time video, meaning that they could incorporate video cameras for recording, videoconferencing, and sophisticated game playing—possibly even movie watching. They'll be smarter, too, assuming more and more of the functions of PDAs and even PCs, including online shopping, e-mail and calendar features, and navigation aids with detailed maps—all accessed via a voice interface. Right now, about half of the transistors in a cell phone go toward interacting with the user rather than processing calls, but Philips's Claasen says the number of transistors dedicated to the user interface will increase by a factor of 10 over the next several years. That will "drive a new cycle of cell-phone buying," predicts Kastner.

And it's not just cell phones that will benefit from microprocessor enhancements. PCs and gadgets will also become friendlier. As devices and the network gain intelligence, they'll require less attention from you. That's critical to their acceptance, says James Meindl, director of the Microelectronics Research Center at the Georgia Institute of Technology. "Until now, we haven't had enough electronics to make the operations of these machines completely simple," he says.

Take televisions. In the sets Philips is planning, says Claasen, fully 80 percent of the computing power on the main chip will be used, not for image-processing chores, but for an adaptive interface that will assemble content from multiple sources geared to your viewing habits and present you with choices in whatever format you're most comfortable with. TVs will become so dependent on computing power, says Claasen, that consumers will soon be shopping for them the way they now select PCs: according to processing speeds, memory size, and communications capabilities rather than their functionality, which will be provided by software and will upgrade itself automatically over the Internet.



And say goodbye to annoyances like having to wrestle your way through four screens of menus to get your PDA to cough up the name you're looking for. Most usability problems will go away, says Aberdeen's Kastner, when electronics start understanding plain English (or Finnish or Mandarin) commands. Speech recognition is often portrayed as a software problem, he notes, but it can in fact be solved with the vast increases in processing power and memory that will be afforded by the coming generation of chips. Appliances and handheld devices that can handle simple spoken commands are already hitting the shelves, and according to Kastner, machines should be able to engage in rudimentary conversation with us by 2010. "With all that power, you can throw multiple algorithms at the problem," he explains. "We won't have all the capabilities of HAL from *2001*, but we'll be a lot closer."

Patrick Gelsinger, chief technology officer at Intel, says the company has already achieved significant improvements in speech recognition in its labs by using multiple microphones to add directionality to incoming sound information and adding lip-reading capabilities via video camera. "If homes are going to go from having four computers to having 400, we've got to make those other 396 a lot easier to use," he says. That increased user-friendliness, he adds, will result in large part from the improvements in microprocessor speed coming down the pike.

SMALL IS BEAUTIFUL

Chip makers continue the march toward miniaturization.

	2003	2005	2007
Smallest standard transistor feature, in nanometers*	90	65	45
Length of structure activating switching, in nanometers	50	35	25
Transistor size, in square micrometers	1.0	.57	.30
Transistors per consumer microprocessor, in millions	180	500	1,000

* By industry convention, each chip-technology generation is known by a standard measurement corresponding to half the distance between cells in a dynamic-random-access memory chip ("DRAM half-pitch").

SOURCE: INTEL

SILICON MAGIC

What sort of huge breakthroughs will allow the semiconductor industry to make these leaps? Actually, none. The experts all pretty much agree: the next three generations of microprocessors, at least, will simply extend the familiar properties of silicon. It's not that there aren't plenty of dramatic innovations at the ready, including more-exotic semiconducting materials like germanium and indium phosphide and techniques for stacking layers of transistors into three-dimensional chips. It's just that the industry can do it with silicon, so it will—because it's cheaper. "Each time someone develops workable new materials or exotic device structures, silicon researchers keep catching up," says Berkeley's Bokor. "There's a very strong interest in industry in making the least-radical change possible."

Chip makers will still have to make a few key modifications to today's methods, starting with the photolithographic process used to chemically etch circuit patterns onto chips. In

DON'T EXPECT TO SEE CHIP MAKERS ADOPT EXOTIC SEMICONDUCTING MATERIALS LIKE GERMANIUM AND INDIUM PHOSPHIDE: THE INDUSTRY CAN BUILD FASTER CHIPS ON SILICON, SO IT WILL—BECAUSE IT'S CHEAPER.

photolithography machines, lenses focus ultraviolet light through a stencil-like "mask" onto silicon wafers coated with a photosensitive material. The photolithography machines used to produce today's chips aren't precise enough to project 65-nanometer features. But new, higher-resolution techniques are being worked out—for example, ultrafine gratings that break up and recombine the light beams so that they reinforce each other at the tiny spots where light is needed and cancel each other out everywhere else. To get to 45 nanometers and below, manufacturers may switch to machines now under development that use either extreme ultraviolet light, which has a shorter wavelength and can therefore be used to etch smaller features, or beams of electrons, which can be finely controlled to etch patterns onto silicon directly, without a mask.

New forms of silicon will also lend a hand. For instance, chips will get a speed boost from silicon that has been deposited over a layer of silicon germanium, whose atoms cause the slightly misaligned atoms of pure silicon to stretch out a bit. This "strained" silicon speeds the journey of electrons through transistors. An additional boost will come from adding a layer of insulating material underneath the semiconducting layers, further enhancing their electrical properties. Microprocessor maker AMD has reported speed jumps of up to 25 and 30 percent, respectively, for the two techniques. IBM and Intel have already begun making chips with strained silicon, and IBM says products combining strained silicon with "silicon-on-insulator" designs could be on the market within several years.

Transistors are also getting a makeover. As the features of transistors shrink, electrons are more likely to stray off their intended course and leak across barriers, even when the transistor is supposed to be off. This leakage wastes power and interferes with transistors' ability to switch between their *0* and *1* states reliably—and it's going to get worse. To plug the leak, the industry is turning to a slightly different transistor design, one pioneered by Bokor and his Berkeley colleagues Tsu-Jae King and Chenming Hu in the late 1990s.

In a conventional transistor, the main point of leakage is a channel of material squeezed between the source and the drain, two larger blocks of silicon that define electrons' principal entry and exit points. A structure called a gate lies atop the channel, like a pontoon bridge across a canal. When a positive voltage is applied to the gate, negatively charged electrons are drawn toward it, opening up a pathway for more electrons to flow through the channel from the source to the drain. The problem, as transistors get smaller, is that electrons can sneak through the thin channel even when the gate isn't charged. The Berkeley group's "fin" design ameliorates leakage by raising the whole transistor above the silicon's surface and reshaping the channel as a narrow, vertical fin that stretches from source to drain like the crossbar of an *H*. The fin sits on an insulating material, which reduces electron leakage, and the gate drapes over the fin, touching it on both vertical surfaces, which doubles the effect of the positive voltage. Intel is already turning to a variation of this design, which should start showing up in microprocessors by 2007.

As a bonus, higher-performing materials and transistor designs make it possible to run chips at lower voltages. This reduces power consumption and, consequently, the risk of overheating, which rises as chips get denser.

THE FAB REALITY

New generations of far more powerful microprocessors are not a done deal. Even if the chips come off assembly lines with all the hoped-for performance, the industry might have trouble keeping their costs low enough that the cell phones and televisions they go into will still seem like bargains. The culprit is the mushrooming cost of constructing a leading-edge chip factory, which is already about $3 billion—out of reach for all but perhaps a dozen companies worldwide.

Of course, the makers of the best-selling electronic products will be able to spread those up-front costs over tens of millions of chips, keeping prices down for at least some products. But rising fab costs could lead to yet another problem for consumers: finding products in stock. Capital investment in the semiconductor industry has fallen by about half in the down economy of the past few years, and observers have issued predictions that the industry will face a shortage of chip-making capacity just as consumer demand for new-wave devices skyrockets.

"Everyone assumes the industry is capable of coming up with whatever capacity is required," says Richard Gordon, vice president of research for the semiconductor group at market research firm Gartner. "But bringing on more capacity is difficult, and with production concentrated in a handful of companies, there's going to be a problem."

But there's good reason to bet the industry will dodge these and any other bullets that come its way. After all, the chip world's ability to prove Moore right year after year without making the daunting leap away from silicon has defied even optimistic expectations. "No matter what the constraints, this industry always pulls off miracles," says Steve Jurvetson, managing director of venture capital firm Draper Fisher Jurvetson.

Just tell your cell phone to keep you posted on the latest developments.

David H. Freedman is a freelance journalist based in Massachusetts and the author of five books. His last article for the magazine was "Pinpoint Weather" (June 2003).

CAN Pfizer DELIVER?

It spends $7 billion on R&D. But can it turn out new drugs at a pace that will keep shareholders happy and the public healthy? The answer may lie in how well Pfizer uses technology to improve the drug development process.

BY DAVID ROTMAN PHOTOGRAPHS BY DAVID BARRY

John LaMattina, Pfizer's president of R&D.

DON'T BOTHER MENTIONING "THE GENOMIC REVOLUTION" these days in the halls of Pfizer's sprawling research and development facility in Groton, CT. Yes, the company's scientists will acknowledge, the latest techniques in genomics and proteomics are interesting and occasionally useful; just don't expect them to revolutionize drug discovery anytime soon. And as Pfizer's R&D executives are equally hasty to point out, the new technologies are expensive—very expensive.

The impatience of Pfizer's researchers with the hype surrounding genomics is not surprising. After a decade of promises and millions of dollars of investments in high-powered new genomic tools, pharmaceutical companies are mired in their most prolonged and painful dry spell in years. Despite skyrocketing R&D spending, which reached $32 billion in 2002, the U.S. industry's output of new drugs has been spiraling downward since 1996. In 2002, the U.S. Food and Drug Administration approved only 17 "new molecular entities"—the agency's jargon for drugs based on a novel active ingredient—the lowest number since 1983, when U.S. drug companies spent only about $3 billion on research and development. (Through the end of October 2003, the FDA had approved 18 new molecular entities.) "There is a research productivity problem, no doubt about it, and it's getting worse," says biologist Anthony Sinskey, codirector of MIT's Program on the Pharmaceutical Industry.

Nowhere is the pressure to end the drought more intense than at Pfizer, the world's largest drugmaker. By most estimates, the company's portfolio of compounds in the late stages of development is fairly healthy compared to the rest of the industry's *(see "Blockbuster Blues," p. 64)*. But Pfizer's sheer size puts it center stage in the effort to cure the industry's productivity woes. In 2003, Pfizer spent $7 billion on R&D, several billion more than its nearest competitor. And it has promised investors it will increase its estimated $45 billion in 2003 revenues at a 10 to 15 percent annual clip. That will require adding the equivalent of several new blockbusters a year. To meet its goals, Pfizer plans to file applications for 20 new drugs over the next five years, says John LaMattina, the company's recently named president of R&D. And, he points out, "no one has ever done that."

Quiet, please: Trays of compounds are part of Pfizer's huge automated library of drug-like chemicals, one of the largest in the world.

Indeed, getting a drug to market remains a high-stakes crapshoot. According to Tufts University's Center for the Study of Drug Development, on average, it now costs $897 million to develop and test a new medicine, and most compounds fail along the way. So Pfizer is placing an emphasis on the use of emerging technologies to optimize this risky and expensive process. The company, for example, is developing an automated system that will rapidly cycle through the traditional steps in the design and synthesis of compounds, hoping to increase the odds of success in drug discovery. To improve human testing of new drugs, Pfizer is seeking cheaper and easier ways to measure whether a potential medicine is effective and whether it might be toxic to patients.

The technologies share an ambitious goal: they're aimed at providing more reliable ways to spot the next blockbuster drug—and to more quickly weed out the thousands of compounds that will eventually prove worthless. They may not be as glamorous as the latest gene-hunting

tricks, but Pfizer is betting these technologies will play a critical role in ending the drought in new drugs. Right now, at least 95 percent of the compounds that enter the drug development process fail to become new medicines, according to LaMattina. "That's our greatest challenge," he says. "It's not a sustainable business model. If we can figure out how to fail only 90 percent of the time, we would double our productivity."

> PFIZER SPENT **$7 BILLION** ON R&D IN 2003, **SEVERAL BILLION MORE** THAN ITS NEAREST COMPETITOR.

Toxicity Software

Pfizer's R&D headquarters in New London, CT, sits across the Thames River from its Groton research facility, overlooking a large estuary flowing into Long Island Sound. But the idyllic scene of sailboats outside his office window does little to soften the intensity of Stephen Williams, Pfizer's executive director of clinical technology. Williams's job is, after all, to worry about failures—especially very expensive ones.

Although failure is a fact of life for drugmakers, the timing of such failures is key. If a compound proves ineffective or possibly toxic while still in the lab, it's no big deal. But if a compound survives early lab tests only to fail years later during large-scale and expensive human testing, it can cause losses of tens of millions, or even hundreds of millions, of dollars, not to mention the time wasted that could have been spent developing other drugs. Less than 20 percent of compounds beginning human clinical testing survive to the end, and, says Williams, the survival rates "for really novel drugs are worse." The "horrifically expensive" failures, he adds, are those that occur in Phase III trials, the final set of human clinical tests that often involves thousands of patients in studies that can last years.

One promising means of avoiding these failures is more accurate tests that detect, at an early stage, subtle biological changes going on in a patient that reflect whether a drug is succeeding, failing, or perhaps proving toxic. Such "biomarkers" can help researchers prove a drug is working. But they can also serve as a cheap, easy, and more effective way to weed out drug candidates. "Just by identifying early and cheaply the failures, you make the [productivity] problem go away," maintains Williams.

The early detection of liver toxicity is one pressing challenge. According to Williams, Pfizer has wasted about $2 billion over the last decade on drugs that failed in advanced human testing—or, in a few instances, were forced off the market—because of liver toxicity problems. Consider the antibiotic drug Trovan, a treatment for severe infections. Pfizer launched the medicine in early 1998 to much fanfare and amid predictions that it would be the company's next blockbuster. Later that year came the news that all drug manufacturers dread: the medicine was apparently causing potentially fatal liver damage in some patients. In 1999 the FDA severely limited use of the once promising medicine.

A potential method for avoiding a recurrence of this nightmare is to use advanced software to spot otherwise invisible

biomarkers. Pfizer mathematicians have developed algorithms to parse out subtle signs of liver toxicity that are missed in conventional analysis of blood tests performed during clinical trials. Normally, reviews of such tests would flag only highly elevated levels of a particular factor. Minor changes are ignored as long as they fall within the normal range. But the new algorithms look for certain patterns within these minor changes. Preliminary testing on a small number of failed drugs showed that such patterns did, in fact exist, says Williams. To validate the findings, the researchers now plan to go back over the company's vast database of blood tests, which covers years of clinical trials and millions of patients, to see if they can further pinpoint patterns correlated with toxicity.

This project will be complex and costly, but if Pfizer could save a substantial fraction of that $2 billion it spent on liver-damaging drugs, it would roughly represent the annual reve-

nues of a new blockbuster product. And for patients, it could mean avoiding the sufferings of another Trovan.

Better biomarkers could also help find drugs for chronic, progressive diseases like Parkinson's, in which symptoms can take years to develop, and for mood disorders like depression, whose symptoms are difficult to quantify. Because it's hard to measure the effectiveness of drugs for these diseases, drugmakers are often reluctant to even attempt to develop them. "If you don't have a good way of measuring [the progress] of a disease, it is almost impossible to develop a drug for it," Williams says.

One unconventional but simple biomarker that could help is the sound of a patient's voice. Pfizer researchers are trying to leverage recent scientific findings that measurable changes in a person's voice can predict his or her sleepiness; they hope to extend that finding to correlate changes in voice to mood swings in patients with depression or to brain damage caused by neurodegenerative diseases. Pfizer's preliminary studies indicate a patient's mood could in fact be gauged by changes in his or her voice. Likewise, the company has encouraging results suggesting that researchers can measure vocal changes in Parkinson's patients. "It is pretty obvious that there are changes," says Williams. "You can hear them. But we showed that we could measure changes before they became audible."

The availability of such inexpensive means of measuring whether a compound is having any effect on a disease could be a boon for researchers testing drugs for such progressive conditions as Parkinson's and Alzheimer's. Instead of waiting, say, five to 10 years as symptoms wax or wane, researchers could quickly and easily determine whether a drug is working. Not only would that allow them to test greater numbers of different compounds, it would, says Williams, encourage far more research on diseases that have long been "handicapped by difficulties in measuring them."

LESS THAN **20 PERCENT** OF EXPERIMENTAL COMPOUNDS **ENTERING HUMAN TRIALS** BECOME NEW DRUGS.

Automating Eureka

The most obvious way to improve the chances of a compound's surviving the drug development process, though, is to start off with the right molecule in the first place. Traditionally, this has meant a mix of good old-fashioned intuition, a vast knowledge of different compounds, and lots of chemical ingenuity.

Take Pfizer's billion-dollar arthritis drug Celebrex. In the early 1990s, John Talley was a medicinal chemist at G. D. Searle, the drug unit of Monsanto, when university researchers discovered the gene that makes an enzyme thought to be involved in causing inflammation. (Pharmacia merged with Monsanto in 2000; in turn, Pfizer bought Pharmacia early last year.) The enzyme was called cox-2, and the finding ignited an industrywide race to produce an arthritis drug that would inhibit it. It's at this point in reciting the story that Talley grows animated; it is when the chemistry really begins.

At a scientific conference, a Searle colleague of Talley's heard about a compound DuPont researchers had synthesized

BLOCKBUSTER BLUES

Is the next Lipitor sitting somewhere in Pfizer's new drug pipeline? The cholesterol-reducing pill—which could soon have sales reaching $10 billion a year—will be a tough act to follow. But Pfizer does have some potential blockbusters that observers are keeping an eye on.

Near the top of the list is a promising medicine to raise levels of HDL cholesterol (the "good" cholesterol). The company plans to combine the new drug with Lipitor, which lowers "bad" LDL cholesterol. Experts also point to a drug for treating neuropathic pain and anxiety that could receive U.S. Food and Drug Administration approval by the end of this year. And Pfizer is testing an interesting antismoking pill.

Despite these drugs' promise, however, some observers say they and other drugs in development are hardly enough to support the huge corporation's growth plans. "In absolute numbers [of new products] and potential sales, it stacks up well," says Shaojing Tong, a financial analyst at New York-based Mehta Partners. But, he says, given that Pfizer's ambition is the double-digit growth of its annual revenues, "it is not enough. You need four or five new blockbusters every year." Adding to the challenge is that patents on many of Pfizer's major products will expire over the next five years, and the drugs will face competition from generic versions. "We don't see Pfizer successfully filling the gap," says Tong.

To prove Tong wrong, Pfizer may need to license the rights to drugs from other companies, or buy companies outright. A number of Pfizer's most important existing medicines—among them Lipitor and the widely used arthritis drug Celebrex—came through such deals. Jim Hall, head of life sciences at Wood Mackenzie, a consultancy in Edinburgh, Scotland, says much of Pfizer's future growth will also likely have to "come through acquisitions and licensing." While the company's R&D group is productive, he says, "the question is, for $7 billion, is it as productive as you want it to be?"

Following is a sample of drugs Pfizer has in development:

CADUET: Combination of Lipitor and hypertension drug Norvasc; new-drug application filed in 2003

DYNASTAT: Cox-2 inhibitor for pain and inflammation; new-drug application expected this year

EXUBERA: Treatment for diabetes; Phase III human trials under way

LIPITOR/TORCETRAPIB: Combination of HDL cholesterol booster and existing LDL cholesterol reducer Lipitor; entered Phase III human trials in 2003

MACUGEN: Treatment for macular degeneration, a leading cause of blindness; licensing alliance with the drug's developer, Eyetech Pharmaceuticals of New York City

PREGABALIN: Treatment for neuropathic pain and anxiety disorders; new-drug application filed in 2003

VARENICLINE: Aid to smoking cessation that uses a new approach to suppressing nicotine craving; began Phase III human trials in 2003

SOURCE: PFIZER (BLOCKBUSTER BLUES)

that seemed to have anti-inflammatory properties. For various reasons, it clearly was not the right compound to make into an anti-arthritis drug, but Talley realized that it could be a starting point, providing critical clues to the chemistry of a drug that might serve as a cox-2 inhibitor. Talley and his coworkers began to chemically tear apart the DuPont molecule to figure out what gave it its biological activity. Armed with that insight, the Searle chemists then began to systematically design a new molecule that would both be effective in blocking cox-2 and have the properties required of any drug, such as lack of toxicity. After more than a year and a half of testing, redesigning, and tweaking more than 2,500 compounds, Talley and his coworkers finally produced a suitable molecule. "The eureka moment comes when you've made the compound," says Talley, who is now vice president of drug discovery at Microbia, a Cambridge, MA-based biotech startup. If you can't make the right compound, he says, the biological knowledge is "just a cool idea."

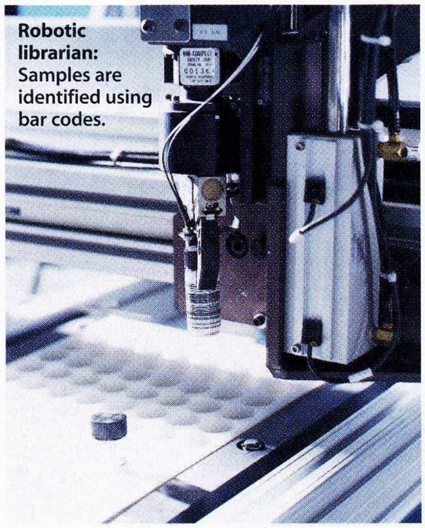
Talley's belief in chemistry as the linchpin of drug discovery is widely shared by Pfizer's researchers and R&D executives. Genomics and other biological tools may provide new disease targets, but the hard—and expensive—job is still to come up with the right compound. "Genomics is not the savior of the industry. The renaissance is in chemistry," says Rod MacKenzie, Pfizer's vice president of discovery research in Ann Arbor, MI.

Pfizer considers its huge library of compounds, housed in a large windowless room at its Groton research labs, the Sistine Chapel of that renaissance. Like any library, this one tells of a collective history—of numerous failures, a few spectacular successes, and most commonly, long-forgotten efforts that never made much of an impression either way. In this library, however, the tales are told in small glass vials, each neatly labeled with a bar code that describes the properties of the compound within and how it was made. Pfizer's chemists around the world can request a chemical, and a robotic librarian scoots down the aisle, retrieving the vial and neatly depositing it on a tray, where it waits to be shipped off.

Pfizer is spending $500 million over the next five years to upgrade and enlarge this collection of millions of druglike chemicals. Not only will the library give Pfizer's chemists ideas and lessons on what works and what doesn't, but it will provide the seed corn for a highly automated, ultrafast new system for discovering drugs. In essence, the system will perform many of the same tasks—chemically designing, testing, and refining a molecule—that Talley and his coworkers handled in inventing Celebrex. But instead of relying on instinct and intuition, the drug discovery machines will rely on automation and brute computing power to quickly perform and interpret a vast number of experiments.

While automation has become routine in pharmaceutical labs, MacKenzie says high-throughput instruments have been limited in the types of chemical reactions they can carry out. That, he says, has changed recently, and automated machines can now produce many more of the types of compounds that interest drug developers. Throw in improvements in the rapid screening of compounds for biological activity and toxicity, as well as improved computational design tools, and an automated system could soon take over much of the drug discovery process, says MacKenzie.

Here's how it might work. A molecule is plucked out of the company's library. The automated system screens it against multiple disease targets and tests it for such things as toxicity. The results are fed back into a computational design and synthesis process, which tweaks the structure of the molecule. The cycle repeats, continually optimizing the compounds based on the results of the screening and testing. Pieces of such a system are already in place, says MacKenzie, and this year Pfizer researchers will begin to link them together into a "closed loop" technology. "It's the old traditional process for doing drug discovery, but it's enabled in a parallel world to move incredibly fast," says MacKenzie. "It is now ready to change the paradigm of drug discovery."



Robotic librarian: Samples are identified using bar codes.

Genomic Gold

No one is sure what exactly lies behind the drug industry's productivity slump, and few are ready to hazard a guess about when it will end. But Kenneth Kaitin, director of Tufts University's Center for the Study of Drug Development, points to several likely causes, including management distractions brought about by a rash of industry mergers and acquisitions and a tightening in FDA regulatory requirements that has made it more difficult to get a drug to market. There is also a suspicion, says Kaitin, that the drug industry spent too much too soon on new biotechnologies, like genomics and proteomics. "It led to increased cost without an increase in productivity," asserts Kaitin. Still, he adds, "there is no going back. The technology is not going away. You need to find ways to efficiently utilize it."

Indeed, it seems certain that any replenishment of the industry's R&D pipeline will be tied to drug companies' learning to better take advantage of these new biological technologies, which have given researchers an unprecedented window into disease mechanisms and how the body works. But as Pfizer and others have learned over the last few years, turning this wealth of information into actual pills is a tough challenge. And future success will likely depend, at least in part, on how well companies are able to use emerging tools like biomarkers and automated drug-discovery systems to make sense of the increasingly complex biological data. The challenge, as Williams puts it, is to find efficient ways to sort "the gold from the lead."

While increasing the productivity of drug discovery is an industrywide challenge, it is hard to overstate the importance of Pfizer in getting it right. At the disposal of this giant organization is an annual R&D budget of $7 billion and an exploding cache of new knowledge of human genetics and biology. Pfizer's attempt to turn these resources into an efficient flow of new and innovative medicines over the next few years is an experiment well worth watching. No one can be sure of the prognosis. But the results are sure to affect the health of us all.

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ten

technologies that refuse to die

In October 2003, *TR* presented a list of 10 technologies that deserve to die.
Now we turn the lens around to examine technologies that have survived obsolescence—with good reason.

By Eric Scigliano Photographs by Fredrik Broden

IN TECHNOLOGY, as in biology, we like to imagine evolution proceeding onward and upward. As new species and technologies appear, their primitive ancestors drop by the wayside, right? Not exactly. Mammals, birds, and flowering plants—all relatively recent innovations—might seem to rule the earth today. But far older designs, from barnacles to crocodiles, are doing just fine in their respective niches, thank you. New species don't always evolve to replace old ones; they also fill vacant niches, which in turn can actually solidify the standing of older species. So it is with technology. ■ Paper and bytes are the classic example. In the early 1980s, at the dawn of the PC age, high-volume electronic storage and transmission—*360-kilobyte floppy disks! 14-kilobit-per-second modems!*—were supposed to make paper superfluous and forests safe. Hah. Electronic data just begat more paper copies. Writers who used to carefully mark corrections on pecked-out manuscripts began printing out one revised version after another. Web surfers started printing out whatever looked interesting. Having data on-screen didn't stop people from wanting to read it, share it, and store it on paper. ■ Like paper, the 10 technologies that follow have seemingly been surpassed and superseded at one time or other, written off as road kill on the highway of progress. But reports of their demise have proved greatly exaggerated. All have survived, and some have thrived, in their supposed obsolescence—not as cult artifacts (everything from buggy whips to eight-tracks has its fans and collectors), but because they fill real needs that their more sophisticated successors don't. ■ Consider these venerable survivors in the pages ahead. »

ANALOG WATCHES Compared to today's digital timepieces, old-fashioned, sweep-hand watches are pathetic one-trick ponies. Digital-watch wearers can check temperature, altitude, and the time in Tokyo, play tunes and games, and send messages. Can wristwatch videoconferencing, Web surfing, and tarot readings be far off? But what digital watches *can't* do, according to sweep-hand proponents, is display the time and context as elegantly and intuitively as an analog model. Children often start out with the digital bells and whistles, then graduate to a sweep hand; then finally, perhaps, they dispense with electronics altogether and acquire an all-mechanical, high-end trophy watch—sales of which have grown dramatically in recent years. In the end, how a device performs its essential job matters more than its extra functions.

DOT-MATRIX PRINTERS Time was, back in the 1980s, that the clickety-click of dot matrix was the sound of progress. Now it's just a memory for most PC users, who want ink-jet or laser printers to churn out family photos and fancy letterheads. But just as dinosaurs evolved into birds—so the theory goes—dot matrix has gotten a jazzier name ("impact printing") and survived as an industrial tool rather than a consumer toy. For accounting firms, banks, and pharmacies with reams of data to print out (and for whom speed, reliability, and economy actually count for more than looks), dot-matrix—er, *impact*—printing still works. Small wonder: today's impact rigs can print up to 2,000 lines a minute, over 500,000 pages a month, for less than a fifth of a cent per page—versus one cent per page and up for ink-jet and laser printers. Epson still offers 12 models, while Okidata advertises 36.

These technologies have survived, and **some have thrived,** because they **fill real needs** that their more sophisticated successors don't.

TYPEWRITERS These original impact printers seem as remote as quills to the generation nursed on PCs. But they too have confounded expectations: in 2002, Americans bought 434,000 word processors and electronic typewriters, according to the Consumer Electronics Association. Even manual machines hold their niche. Olympia and Olivetti still make classic machines. Consider the advantages: no viruses to catch, no hard drives or software to get corrupted, no batteries to run down. Typewriters do one thing computers can't—fill out printed forms—and are faster at addressing envelopes and other one-shot jobs that usually don't entail revisions. Affection and habit also sustain old machines. One Seattle typewriter repairman says that aging writers who "prefer simplicity and don't want to learn computers" are what keep him in business. And you needn't worry about your system going obsolete if it already is.

BROADCAST RADIO **This medium was declared D.O.A. after commercial television stormed the scene in the late 1940s. TV stole radio's top shows, national sponsors, and central place in the home. But this erstwhile dinosaur was quickly repositioned to exploit the next decade's social and technological changes. Portability was key: transistors and cars made radio the mobile medium of an increasingly mobile society. Suburbs, superhighways, and longer commutes provided a vast captive audience. Mass-market youth culture, disc jockeys, and, later, talk jocks opened new franchises. With TV glomming the national market and local newspapers folding in droves, radio became a more local medium, airing hometown news, sports, weather, and traffic reports. Now, ownership consolidation and cookie-cutter programming are reversing that trend; and mobile-Internet games, MP3s, and instant messaging threaten radio's franchise as the real-time, go-anywhere companion. But hey, radio has been pronounced obsolete before.**

PAGERS The teens who made these devices essential fashion accessories in the early '90s graduated to cell phones, and even RadioShack stopped selling them. But pager sales rose in 2002, contrary to industry expectations. Some institutions still rely heavily on pagers: police departments, whose officers' hands and gun belts are often too full for cell phones; hospitals, where cell-phone signals would interfere with diagnostic equipment; and schools, which can't readily afford cellular service. And pagers still beat cell phones in some ways. They're cheaper, with no roaming charges. They need far fewer transmitters than cell phones but still provide better coverage, so they work in the dead spots between local "cells." And pagers tend not to jam up in emergencies the way overloaded cells may. Best of all, they are far less likely to make you crash your car or turn you into a yakking boor. And now, two-way text messaging makes them a plausible alternative to phones.

REEL-TO-REEL TAPE Cassettes supplanted reel-to-reel for home recording in the 1960s; now cassettes have given way to CD players and recorders. So surely tape is as defunct as the dodo? Not quite. Many analog tape sizes, from two-track .63-centimeter (quarter-inch) to 24-track five-centimeter (two-inch), are still available. Some recording engineers still swear by tape, which they claim captures nuances of sound that even the most byte-heavy digital recorder can't—just as ardent audiophiles still swear by vinyl records played on $10,000 laser turntables. And a few firms still offer two-track 1.27-centimeter (half-inch) players. "The market's pretty steady," says Dan Palmer, former product-development director at the high-end manufacturer Otari. "Archiving" is what drives it: customers buy the players to transfer precious taped works to digital.

VACUUM TUBES Audiophiles have sustained another technology that's even older than magnetic tape. In the 1970s, compact, energy-efficient transistors boded to replace vacuum tubes entirely. But transistors couldn't satisfy some guitar players and hi-fi cognoscenti. "We use vacuum tubes because they *sound* good," says Victor Tiscareno, a trained violinist and vice president of engineering at Red Rose Music, a maker of high-end home audio systems. Low-distortion, solid-state-transistor sound "looks lovely on an oscilloscope," he explains. "But what we measure and what we hear aren't the same. Vacuum tubes just sound more human, more lifelike." And after Armageddon, they may be the last amplifiers left standing; rumor has it the U.S. government still keeps backup tubes in case an electromagnetic pulse wipes out vital communications circuits.

FAX MACHINES **With e-mail and scanners nearly universal, these clunky devices should be obsolete: why deal with paper jams and**

busy signals? Yet American consumers bought over two million fax machines in 2002. Fax is still the fastest way to transmit on-paper images, documents, and marked-up text. While some occupations (journalism) have moved overwhelmingly to e-mail, others remain stuck on fax. Real estate, with its endlessly amended offers, counter-offers, waivers, and warranties, still runs on it. Lawyers also remain big faxers. The rest of us grimace and use it when we have to.

MAINFRAME COMPUTERS These big rigs costing over $1 million apiece have been dismissed as dinosaurs—big, lumbering, expensive ones at that—since the PC arrived. But the explosion of Windows networks and Unix servers obscured the fact that banks and other institutions have continued relying on mainframes for large-scale data processing. And "big iron" has seen a minor resurgence in the new millennium: IBM's mainframe sales rose in 2001 for the first time since 1989 and have continued to increase. Speed, security, and reliability are also motives: IBM claims a once-in-30-years failure rate for its latest model, the z990.

FORTRAN Forty-seven years after IBM unleashed it, Fortran (*for*mula *tran*slation), the original "high-level" programming language, would seem to be the infotech equivalent of cuneiform. But it's still widely used, especially in scientific computing. Why has this Eisenhower-era veteran outlasted so many hardware and software generations? "It's partly the learning curve," says Hewlett-Packard Laboratories' Hans Boehm, former chair of the Association for Computing Research's special-interest group on programming languages. "For some people it's good enough, and it's hard to let go of something once you learn it." Adaptability and compatibility, which made Fortran the programmers' lingua franca in the 1960s and '70s, are also key to its viability. Major upgrades have boosted efficiency and added features while preserving old versions intact. So a vast number of tried-and-true Fortran 77 programs jibe with the current Fortran 90. Microsoft, take note.

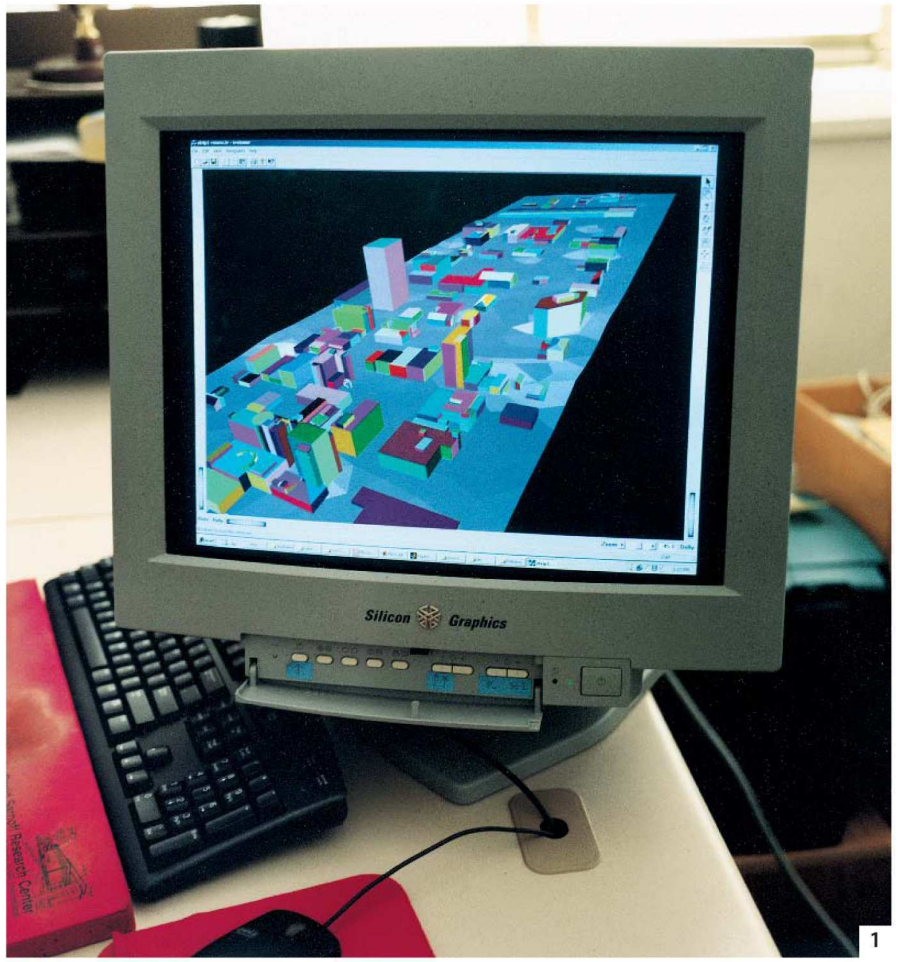
Eric Scigliano is a science and technology writer based in Seattle, WA.

DEMO

SEAMLESS SURVEILLANCE

What if monitoring an airport or city was as easy as joysticking through a video game? Rakesh Kumar's team at Sarnoff is creating big-picture views from myriad individual video feeds. PHOTOGRAPHS BY BETH PERKINS

VIDEO CAMERAS ARE proliferating; they're everywhere at airports, urban centers, and government buildings. But how do you tackle the tedious job of actually watching all these boring, narrowly focused video feeds? Sarnoff, the former RCA Labs now owned by SRI International, is building a solution—a system that combines video from many cameras into a 3-D model of an area. "Instead of watching the world through a soda straw, this is essentially taking video and putting it into context," says Rakesh Kumar, a computer scientist who developed the technology as director of Sarnoff's 14-member media vision lab. The result is called Video Flashlight: it's like playing a video game, except the scene is of real events in real time; grab a joystick and you can swoop down hallways and fly around buildings, immersing yourself in a scene. The technology has a rich legacy: RCA was a pioneer in television technology, and its laboratory was a key source of World War II–era electronics innovations. Today, Video Flashlight is getting tested as a security tool at government buildings. At Sarnoff's labs in Princeton, NJ, Kumar showed *TR* senior editor David Talbot the latest in surveillance.



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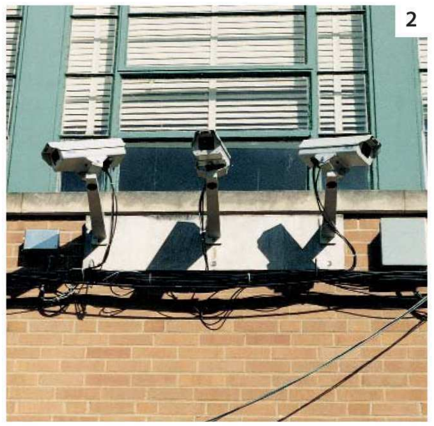
1. The critical first step: creating a 3-D computer model of the area to be monitored. This forms the background on which live video feeds are superimposed. Kumar introduces the modeling-project leader on his team, computer scientist Steve Hsu.

Hsu taps a few keys and shows a current work in progress, a 3-D model of downtown Baton Rouge, LA. This model was made using an established technology: airplane-mounted laser scanners that record topographical features. Models can also be made using video images—and even ordinary 2-D digital photographs—that are rendered by software into 3-D.

Once the data is gathered, the raw 3-D shapes get a more realistic look from software that "paints" features like windows and doors, using information gathered from photographs. It takes days to build a model, but "it used to take a skilled artist weeks," Hsu says. "Our goal is to get to where I can model a small town in six hours." Such speed is critical for jobs like rapidly installing video surveillance on urban battlefields.

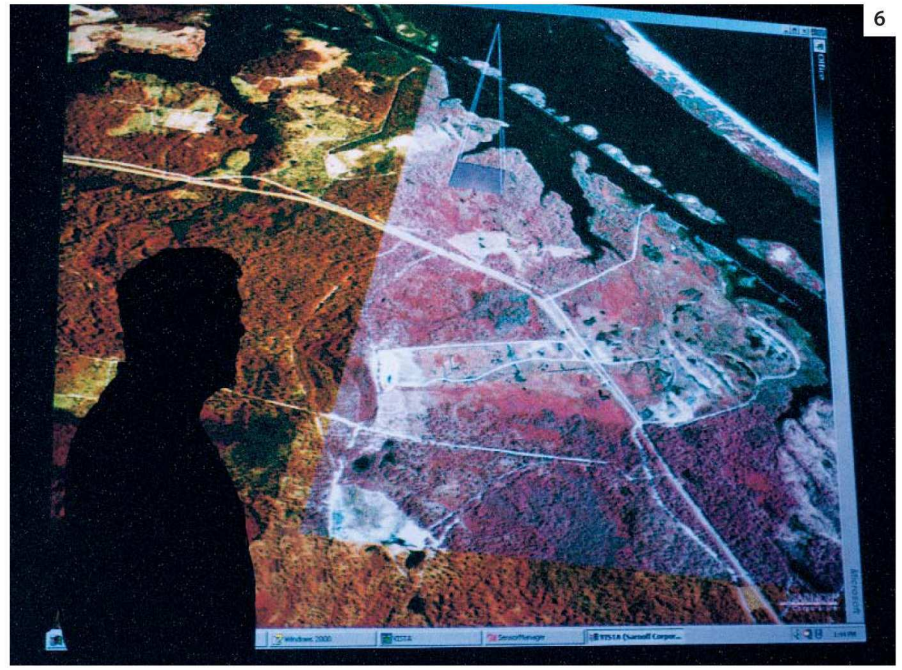


2

2 - 3. Camera placement is the next step. A computer analysis of the 3-D model suggests ideal placements on building facades or in hallways to optimize coverage; "Any old camera will do," Kumar says. As part of the system deployed at the Sarnoff site itself, cameras (2) are installed on an exterior wall. The enormous amounts of data gathered by these cameras are stored inside the Sarnoff facility in banks of digital video recorders (3). With this information, the monitoring system allows security guards to instantly review old events.

3

4. It's game time. Demonstrating how the system works with 12 fixed cameras around a Sarnoff building, Kumar hands the controls to Aydın Arpa, whom he calls the "graphics guru" of his group. Arpa grabs the joystick for a view of Sarnoff's main entrance (4). On the display, data from each of the cameras is superimposed on the model. "The cameras act like a flashlight, illuminating the static model with live video," Kumar says. As Arpa swoops around and zooms in and out of the scene, software keeps video images seamlessly aligned with each other and with the 3-D model. This allows Arpa to "fly" around an object and even view it from different angles. When the video cameras pick up new or moving objects, a Sarnoff technology called "pyramid processing" enables automatic detection and tracking of new people or other elements



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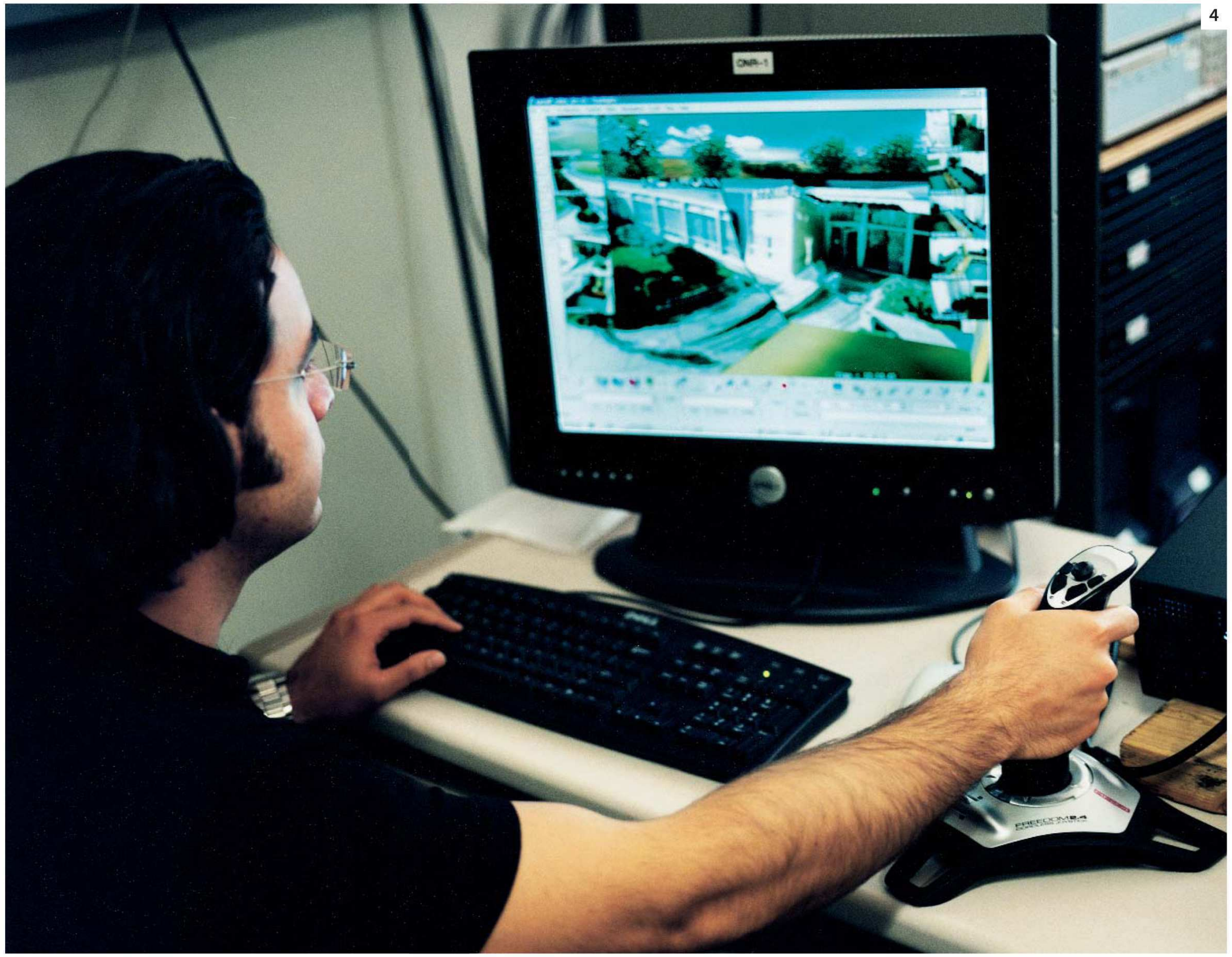

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in a scene. The Sarnoff system also merges interior and exterior models; this provides a way, for example, to follow a person as he or she enters a building. Sarnoff is working on software that will transform 2-D video images of people and new objects into rough 3-D versions to make them look realistic as a guard "flies" around them.

5 - 6. The current technology requires fixed cameras. Kumar has bigger ambitions: handling video from cameras in motion, and linking video surveillance across the globe. In an experimental system, a Sarnoff chip (5) processes video feeds from cameras in motion, even those attached to airplanes. The chip also aligns moving video feeds with digital maps using both Global Positioning System information and software that "matches features the camera sees on the ground with features in a database," Kumar says. The results are visible on a wall screen (6), where the field of view of a plane-mounted camera shows up as a pyramid shape on a map of the New Jersey coastline. The result is Video Flashlight writ large: a joystick sweep can pull you back from the Sarnoff campus and then transport you clear across New Jersey—and eventually, the world. TR

Valid Voting?

BY ERIKA JONIETZ | Photograph by Lenny Gonzalez

TECHNOLOGY REVIEW: Electronic voting is a relatively new concept in the United States. How do these systems work?
DAVID L. DILL: We have touch-screen machines, or more generally, direct-recording electronic machines. The voter puts in the vote either via a touch screen or a knob, and the ballots are recorded electronically in the machine's memory.

TR: Wouldn't that make counting votes faster and more accurate than other systems, like punch cards? Why object?
DILL: The problem with this technology is the voter can't observe the record that it made. So a voter could vote for candidate A, and the machine could record a vote for candidate B. There is no way that anyone can tell that that voter voted for candidate A. No matter how you conduct a recount, you're going to get what appears to be a vote for candidate B—we're unable to do a meaningful recount.

TR: Are errors and fraud really more likely with these machines, though?
DILL: Of course, there has been election fraud with paper ballots. Sometimes what the debate gets down to is, people admit that electronic voting is completely insecure but say that paper is insecure as well. It really depends on how well your election is run. People have had a hundred-plus years of experience with paper ballots. It's pretty well known how to maintain the integrity of a paper-ballot election.

The problem with the touch-screen machines is, regardless of how diligent election officials are, there can be errors or fraud committed by the programmers or anybody who had access to the software before it was installed on the machine.

Now, I suspect that the most frequent problem we'll see—or more worryingly, the most frequent problems that will occur that we don't see—will be errors, just accidents, causing changes in the vote.

TR: Intentional fraud wouldn't seem to be much of a concern, then.
DILL: If you think about it rationally, there's a set of questions. Who might commit fraud, and what is their level of motivation? Can they get technical experts to do it? What kind of money or other resources can they muster? And if you think about people who would want to alter the results of elections—particularly at the national level—they can bring tremendous resources to bear. We're talking about foreign governments, organized crime, major government contractors—people who have a major financial stake in who is controlling the U.S. government.

There are certainly case studies of these things happening in foreign countries, but in our own country, if you look at Watergate as an example—suppose those guys weren't trying to bug the Democratic Party headquarters but were actually going after the electoral system through a voting company? It's a pretty scary prospect, and it seems to me from examining the system that there's little likelihood that somebody committing that sort of fraud would get caught.

TR: Voting-machine companies face severe criticism for the security of their software. But couldn't these machines be made secure enough to avoid that scenario?
DILL: As a computer scientist, I don't think they can make it secure enough, no matter what their procedure, or how they design the machine, or how the machines are inspected at independent laboratories. I have, however, attempted to find out what the actual processes are, and they are much worse than what is achievable. The place where we learned the most was when [touch-screen-voting leader] Diebold's source code and many of their other files were placed on the Internet. They were examined by researchers at Johns Hopkins University and Rice University. And various possibilities for external attacks—even by voters—came up in that review.

I don't know how concerned to be about that. It could be that these systems have major weaknesses that they don't need to have. That was certainly the case with Diebold. And the various regulations, the testing laboratory, the logic and accuracy tests are not solving the problem.

DAVID L. DILL

POSITION: Professor of computer science, Stanford University

ISSUE: Electronic voting. U.S. state and local election commissions are increasingly adopting computerized voting machines. But many believe the systems open the door to increased voting error and fraud.

PERSONAL POINT OF IMPACT: Crafted the Resolution on Electronic Voting, advocating a permanent paper record of each vote that allows voters to verify their own ballots; the resolution has been endorsed by several top computer security experts

TR: Diebold has sold touch-screen machines to Georgia, and has a contract with Maryland?
DILL: Yes. *[Note: A Diebold spokesman says these machines use updated source code, different from that posted on the Web.]*

TR: What is required to avoid fraud or large-scale errors?
DILL: I wrote the Resolution on Electronic Voting with help from other computer scientists. We tried to make the most general requirement we thought would work. So we asked for a voter-verifiable audit trail—a permanent record made of the vote that the voter can check is accurate, and that is available for a recount. Now, the only way to do that that is proven at this point is to use paper somehow. You can have a fully manual process, in which case the ballot that you fill out is that voter-verifiable audit trail: you have the ability to make sure it's correct because you're actually filling it out. The same for an optical-scan ballot or punch card.

With the touch-screen machine, the solution is to add on a voter-verifiable printer. That prints a copy of your vote, and you get a chance to look at it, make sure that it correctly registers your vote, and reject it if it does not. Then that paper record goes into a locked ballot box. It's important that the voter not be able to take it out of the polling place because that facilitates vote selling or coercion.

There's nothing inherently wrong with having computers in the process. You just have to do it right. The Help America Vote Act, a national election reform law passed in 2002, says something about a manual audit capacity. And California's Prop 41 says that the machines have to print paper copies of the ballot either during the election or right after the polls close. The problem with the second solution is, if we go back to the scenario where the voter votes for candidate A, and a vote is recorded for candidate B, anything that's printed after the polls close cannot be verified by the voter. You'll end up with a copy of what's in electronic memory. Your recount is always going to come out the same as your electronic copy, and it will fail to catch errors in recording the votes.

TR: So what is currently the best option?
DILL: It's a really difficult question because people have a very long wish list for electronic voting—or for any kind of voting. It's hard to satisfy all of these requirements. But given what I know now, I think the best option is a precinct-based optical-scan system—with some special device such as a touch-screen machine for use by people who cannot use that system. In a precinct-based system, the voter himself puts the ballot into the machine which reads it. The advantage is that the machines can be programmed to reject ballots that have stray marks or too many votes, so that the voters can correct them then and there.

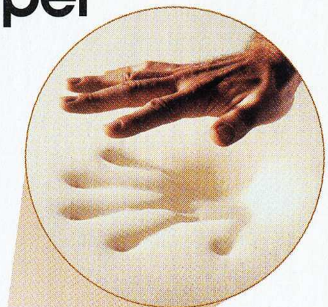
The other option is to go with direct-recording electronic machines with a voter-verifiable printer. I really only have two concerns about that. One is that it is even more expensive than the touch-screen machines, which are pretty expensive. The other concern is that it's a relatively new idea that hasn't been tested a lot in actual elections. I think we should have the pioneering counties try it out and then, once we understand how that system works better, consider deploying more machines.

TR: The U.S. Department of Defense has a pilot program using Internet voting to help soldiers stationed abroad vote more easily. Might we all vote that way someday?
DILL: They've succeeded in finding the only idea worse than electronic voting in precincts. Even people who disagree with me about touch-screen voting say that Internet voting is a bad idea. I understand the need to make sure that people in the services vote. And I understand the problems they have now with getting absentee ballots. But I think Internet voting is not the right solution. I'm too busy with my particular battle to combat that, but I hope somebody is able to get it killed. TR

Sleep Better™ Technology

Get in the zone with the mattress topper that molds to your body's contours

The Memory Foam Ultra mattress topper is cut into a grid pattern combining six different zones for variable support and a better night's sleep.

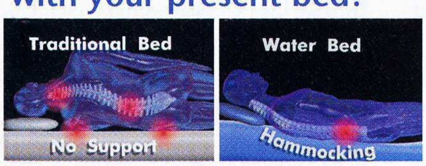


The 2-inch thick temperature-smart foam adjusts to your shape.

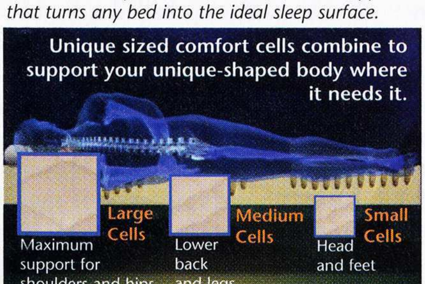
It's 3 a.m. You have exactly two hours until you have to get up for work, and you still can't seem to fall asleep. At this point, the phrase "tossing and turning" begins to take on a whole new meaning for people whose mattresses simply aren't giving proper support anymore. Your mattress may dictate your quality of sleep. Even if you merely suspect that your mattress may be outdated, that's when you need to take action. Some mattresses fail to support your spine properly, which can result in increased pressure on certain parts of your body. Other mattresses, sporting certain degrees of visco-elastic foam, can sometimes cost you well over $1000. Now, one of the world's leading manufacturers of foam products has developed an incredibly affordable mattress topper that can actually change the way you sleep. Introducing the future of a better night's sleep: The Memory Foam Ultra mattress topper.

Sleep Better™...Wake up to a better morning. The Memory Foam Ultra mattress topper is designed to give you a better sleep surface. Not only does it support each region of your body, but it's also temperature sensitive. With its various-sized "comfort cells," the 2-inch thick Memory Foam Ultra mattress topper combines six zones to support specific body area weight, which promotes a better night's sleep. The largest cells support your lower back and midsection, while the medium-sized cells support the shoulders, lower back and legs. The smallest cells support your head and feet. Combined, these zones provide variable support from head to toe. By using visco-elastic foam, the Memory Foam Ultra mattress topper also molds to your body contours to help prevent tossing and turning during the night. When you lie down on this amazing material, the heat and pressure sensitive foam reacts to your body's weight and temperature, so that it molds to your exact body shape. This means that whether you sleep on your back, stomach or side, your weight is evenly distributed and your spine remains in a neutral position. Other surfaces support your body at the shoulders, hips and legs only. This causes your spine to sag in other areas, which can often result in discomfort, and even back pain. You'll wake up rested, relaxed and ready to take on the day. Anyone who suffers from insomnia and back pain due to mattress discomfort can benefit from this technology.

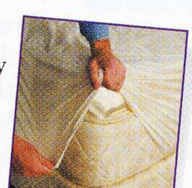
What could be wrong with your present bed?



The ideal position is a neutral body posture in which the different parts of the human body are supported individually and evenly. This is the secret behind Memory Foam Ultra, the mattress topper that turns any bed into the ideal sleep surface.



FREE heavyweight mattress pad included. Included with the Memory Foam Ultra mattress topper is a fitted mattress pad. It's heavyweight and quilted, and made of 200-count 100% cotton with a 14-inch deep stretchable skirt to fit a mattress up to 21 inches thick. The size of the mattress pad is determined by the size mattress topper you order.



Try it for yourself today! The Memory Foam Ultra mattress topper can change the way you sleep. Promote proper spine positioning, while enjoying relief from insomnia and back pain with this full-body support. It comes with a 5-year manufacturer's limited warranty and TechnoScout's exclusive in-home trial. If you are not completely satisfied, simply return it within **60 days** for the full purchase price.

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Cooling Off Computers

BY CORIE LOK

As the semiconductor industry continues its quest for smaller and faster chips, it's running into a heat wave. With more transistors crammed onto them, chips are using more power and hence getting hotter—and the heat is becoming more concentrated and harder to dissipate. The problem has become so severe that, for chips used in applications such as servers and laptops, gains in processing speed have started to do some dissipating of their own.

Cooligy, a startup out of Stanford University, says it has a solution: a micromachined cooling system that works much like the radiator in your car. Cooligy claims its liquid-based system can remove at least 30 percent more heat than existing cooling technologies in high-performance computers while replacing noisy, high-speed fans with far quieter ones. "We have a way to break through the heat barrier for many generations [of faster chips] to come," says Dave Corbin, Cooligy's CEO.

Cooligy was founded in 2001 by three Stanford mechanical engineering professors who had been working on a liquid cooling system—combining their expertise in heat transfer, microfluidics, and micromachining—since 1998. With two rounds of venture funding totaling $15.8 million in its pocket, Cooligy is making prototypes that it will demonstrate to makers of workstations, servers, and high-end PCs. Such manufacturers spend $250 million on existing cooling systems, and Cooligy hopes to have customers for its product by the end of this year.

COOLIGY

HEADQUARTERS: Mountain View, CA

UNIVERSITY: Stanford

INVESTMENT RAISED: $15.8 million

LEAD INVESTORS: Mayfield; Mohr, Davidow Ventures

KEY FOUNDERS: Ken Goodson, Tom Kenny, Juan Santiago

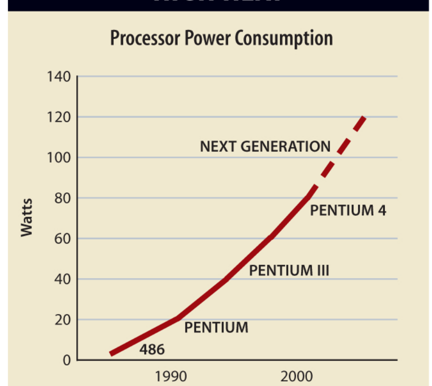
In a typical PC, the microprocessor is cooled by heat sinks—pieces of metal attached to the chip that conduct heat away—and high-speed fans blowing directly on the metal. But heat sinks are not particularly efficient, and one of the few ways to boost cooling capacity is to add more fans, which make computers heavier and noisier. The heat pipes used in laptops and workstations are slightly more efficient. The end of the pipe near the chip contains a fluid that boils; the vapor moves on its own to the other end, away from the chip, where it releases its heat, condenses, and trickles back to its starting point. But these cooling technologies are reaching their limits in devices such as servers and laptops, causing the annual increase in chip processing speed to slip to as little as 30 percent, down from about 60 percent a few years ago. Soon enough, this slowdown will hit desktop PCs, too. And heat is to blame, says Linley Gwennap of the Linley Group, a technology analysis firm in Mountain View, CA. "An advance in cooling technology could help us get another jump in performance, or else we'll be stuck."

Cooligy is trying something completely different. Its technology consists of a piece of silicon with tiny channels etched into it. The device sits on top of the microprocessor, and a fluid flows through the channels, picking up heat directly from the chip. The fluid is then pumped through a tube and into a radiator located at the computer's outer edge, where the heat is dissipated by fans. The cooled liquid then returns to the microchannels and begins the process anew. The key is the novel design of the pump that propels the liquid through the system: a glass disk with tiny pores through which water flows when an electric field is applied, it has no moving parts.

While other academic researchers have previously developed radiator-based cooling systems, they have used large, mechanical pumps that won't easily fit inside a computer, says Ken Goodson, one of Cooligy's cofounders. As a result, the technology never went anywhere. "Cooligy's edge is in their pump, the way they collect heat from hot spots and the way their microchannels are manufactured," says Sean Lee, an electrical engineering professor at the Georgia Institute of Technology.

Although Cooligy is currently focused on high-end computers, it sees them as just a starting point. Corbin's goal is to turn Cooligy into a high-volume manufacturer selling to all major computer makers. With motherboards getting hot enough to fry an egg on, Cooligy's technology could provide just the relief chip and computer makers have been looking for. TR

HIGH HEAT



OTHER COOLING STRATEGIES

COMPANY	TECHNOLOGY
Active Cool (Ashkelon, Israel)	Thermoelectric cooling for PC processors
Cool Chips (Gibraltar)	Solid-state heat pumps based on thermotunneling to cool electronics
Isothermal Systems Research (Clarkston, WA)	Direct spraying of fluid onto electronics

SOURCE: COOLIGY (HIGH HEAT)

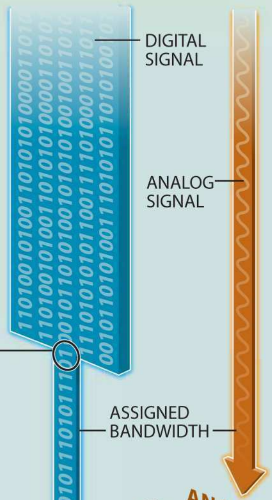
High-Definition Television

Even the lowest-resolution computer screens provide better images than today's best analog televisions. No wonder television broadcasting is going digital. Digital signals carry more information than analog ones, the images they provide are sharper, and they can be displayed in the wide-screen format typical in movie theaters. The U.S. Congress has set December 31, 2006, as the target date for all domestic TV broadcasts to be sent digitally. (It could be extended, though, until 85 percent of homes have TVs that can receive the signals.) **TEXT AND ART BY 5W INFOGRAPHIC**

SIGNAL TRANSMISSION

DIGITAL VS. ANALOG

HDTV signals are transmitted as constant streams of *0*s and *1*s, while analog signals are sent as continuously changing waves. The digital HDTV signals stay more consistent over longer distances and can carry more data, which will enable them to handle not just audio and video but also interactive features such as game-playing.



COMPRESSION

HDTV signals carry five times more data than analog signals; to fit within the bandwidth assigned to television broadcasting, that data must be compressed.

MPEG-2

The compression algorithm, MPEG-2, works in two ways: within frames and between frames.

Within frames: The algorithm strips details from the image, selecting those small enough that the human eye won't perceive their absence.

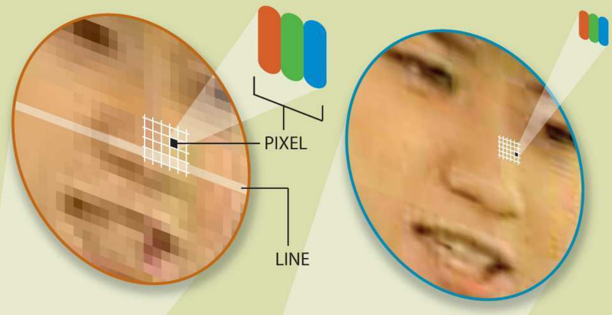
Between frames: MPEG-2 compares the digital information in adjacent frames and discards information that is redundant from one frame **(A)** to the next **(B)**.

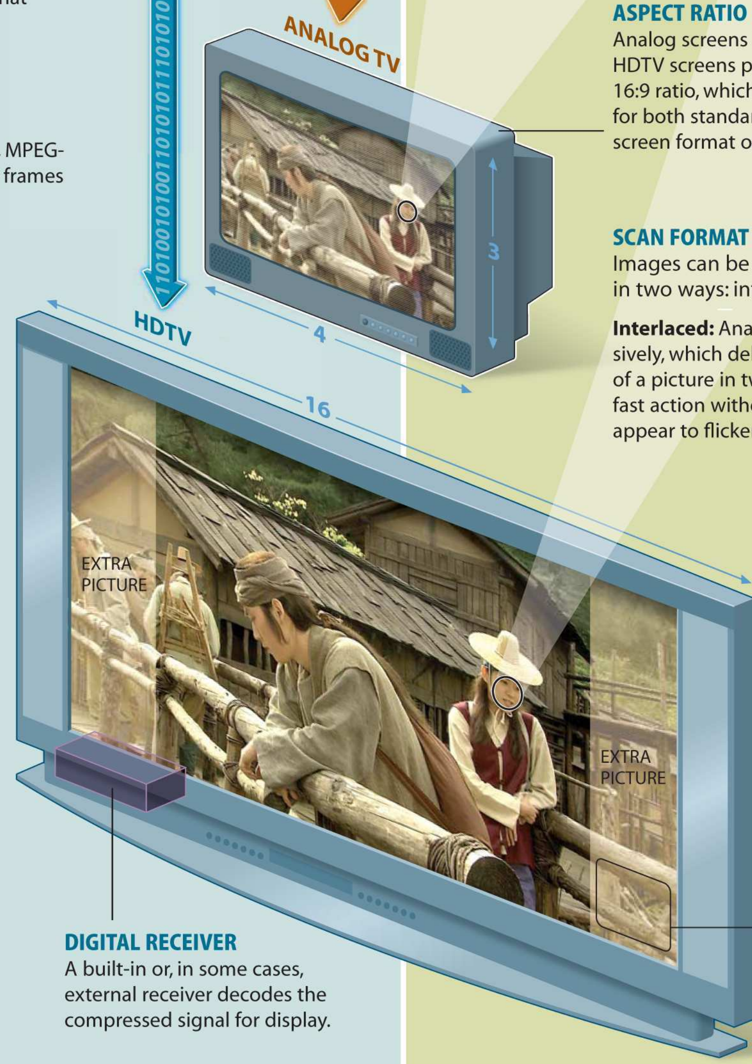
REDUNDANT INFORMATION DISCARDED

IMAGE DISPLAY

PIXEL AND LINE RESOLUTION

HDTV screens display higher-resolution images than analog TVs. First, the screens contain pixels that are 4.5 times smaller than those of analog screens. Second, an image is scanned onto the HDTV screen with up to 1,080 lines, compared to 480 lines with analog.





ASPECT RATIO

Analog screens have a 4:3 width-to-height ratio. HDTV screens provide extra image with their 16:9 ratio, which lets them display images filmed for both standard TV broadcasts and in the wide-screen format of movies and HDTV broadcasts.

SCAN FORMAT

Images can be scanned onto a screen in two ways: interlaced and progressive.

Interlaced: Analog uses interlaced scan exclusively, which delivers the odd, then even, lines of a picture in two passes. The format reproduces fast action without blur, but static images can appear to flicker.

Progressive: HDTV accommodates interlaced and progressive scan, which delivers all of the lines in one pass. The sharper images occupy considerably more bandwidth.

DIGITAL RECEIVER

A built-in or, in some cases, external receiver decodes the compressed signal for display.

Deciphering Cars

THE LITTLE RED LIGHT IN MY 1993 PLYMOUTH Grand Voyager said "Check Engine." I appreciated the suggestion. But I had no idea what it meant. ▪ The van, you see, had been a gift from my wife's sister. It had 187,00 kilometers (116,000 miles) on it when I picked it up in Chicago for the long drive to Boston. Halfway back the engine almost caught on fire; when I arrived two days later, I discovered that it needed nearly $5,000 in repairs. Three days after that work was done, the transmission died.

All in all, this "free" van had cost me nearly $8,000, and now something else was wrong. What was it? I didn't trust the dealership to tell me what was really going on: I felt that they were dishing out the bad news one broken part at a time, so that I wouldn't realize the full scope of my problems. So instead of turning to the experts, I turned to the Internet. I was troubled by what I learned—not about the state of the old van, but about how limited my access was to information about a product that I owned.

A lot of people are intimidated by the idea of trying to repair a modern car. What's so discouraging, apparently, is the "car computer"—the electronic brain that controls everything from the emissions system to the battery charger. People who once had no problem doing tune-ups with strobe timing lights see these electronic boxes and just give up.

But in fact, the car computer is your friend—constantly monitoring whether anything is going wrong.

At the suggestion of a friend, I typed the keywords "Voyager" and "Diagnostic Trouble Codes" into Google. This landed me at a Web site that offered step-by-step instructions on how to get my car's computer to spill its secrets.

Different cars have different "secret handshakes" that you need to know to extract the diagnostic codes. On some GM cars, for instance, you turn on the the car's ignition then hold down the "Off" and "Warmer" buttons on the climate control system until a special light appears on the instrument panel. For other cars you need a device called an onboard diagnostic (OBD) scanner; these gizmos cost anywhere from $20 to $250. For my Plymouth van, you read the codes by turning the ignition switch on and off two times in a row, turning it back on, and counting the number of times that the "Check Engine" light flashes.

The issue here is our rights as owners of technology: if a car's onboard computer makes a diagnosis, we have the right to know it.

In theory, knowing these codes should let you fix your car just the way the pros do. Just ask the car computer what component is malfunctioning, and then replace it. And if the computer can't figure it out, you replace the computer itself! This simple logic will let you diagnose the vast majority of common car problems.

But there's a problem with this approach: you need to know those diagnostic codes. Without them, you're nowhere. And as it turns out, even though you've paid tens of thousands of dollars to buy your car, you have no right to know what those codes really mean—or how to get them out of *your* machine.

Automakers, independent service shops, and AAA have struggled for years over who has rights to these diagnostic codes. Clearly, by controlling access to this information, automakers can give their own dealers an edge in servicing their own vehicles—or they can force independent garages to sign up for training and pay hefty license fees.

In 2001, the U.S. Congress threatened automakers with the Right to Repair Act, which would have forced them to reveal their codes. The legislation was scuttled in 2002 when automakers promised that they would share their technical information. The legislation, officially designated HR 2735, was reintroduced in the House of Representatives last July.

Not surprisingly, automakers oppose the legislation. "It is not necessary," says John Trajnowski, a principal staff engineer at Ford Motor. "We are making all of our information available now." Consumers and independent repair shops can purchase three-day access to Ford's Motorcraft Web site for $19.95.

Trajnowski contends that the legislation "is being sponsored primarily by after-market-parts manufacturers," who want to force carmakers to reveal their "proprietary control strategies" for sensors, controls, and other high-tech car equipment. This would make it easier for third parties to make clone parts.

But even if the legislation has such a hidden purpose, it's irrelevant. The real issue here is our rights as owners of technology in the digital age: if we buy a car that has an onboard computer, that computer should act in our best interests. If it makes a diagnosis, we have a right to know it. Our tools shouldn't hide information from us in order to enhance somebody else's revenue. AAA has taken a similar position and is strongly supporting HR 2735. With luck, it will pass before the end of the session this fall.

As for my van, the computer said that the problem was with the oxygen sensor. But the fan control relay was also acting up. And there were possibly problems with the internal logic module. I decided that things were going to keep breaking, so we halted all repairs and traded in the van for a 2004 Honda Pilot. We got $500. TR

Simson Garfinkel is an incurable gadgeteer, an entrepreneur, and the author of 12 books on information technology and its impact.

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People and organizations mentioned in this issue

Al Gross at his ham radio station.

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Walk the Talk

A young ham radio enthusiast pioneered wireless telecommunications with the walkie-talkie. **BY LISA SCANLON**

IN THE LATE 1930S, AL GROSS, A teenage ham radio enthusiast in Cleveland, OH, built some handheld devices that allowed his friends and him to communicate on an unused portion of the radio frequency band; he named his creation the "walkie-talkie." Although Gross's innovation later played an important part in World War II, neither it nor his other major inventions became commercially successful until many years after his patents expired.

As an electrical engineering student at Cleveland's Case School of Applied Sciences, Gross discovered a way to cause miniature vacuum tubes to operate at about 300 megahertz, a relatively unexplored high frequency. By 1938, he had built battery-operated models that allowed him to communicate with radio operators more than 45 kilometers away.

Early in World War II, the U.S. Office of Strategic Services learned about Gross's walkie-talkies and called the young inventor to Washington, DC. The office asked him to develop a system that would allow Allied agents in Germany and occupied countries to communicate with pilots flying overhead. Because the system operated at a virtually unused high frequency, operators could transmit military intelligence without being detected by enemy shortwave-radio operators.

After the war ended, Gross founded Citizens Radio to commercialize the technology. The company's customers included the U.S. Coast Guard and farmers, but the walkie-talkie wasn't a commercial hit.

Meanwhile, Gross built other communications devices, including cordless telephones and personal paging systems. Gross had begun developing the pager during World War II, when he designed a device that could be attached to dynamite on the ground and signaled to ignite it from an airplane flying nearby. Gross thought that a modified version could be used to page doctors. He built a prototype device in 1949, but when he demonstrated it at a medical convention, his audience wasn't interested. "They said it would interfere with the patients, and it would interrupt their leisure time, like golf games, I suppose," Gross said during a 2000 interview on Canada's CBC Radio One.

Although Gross's key inventions didn't become popular until after his patents expired in the early 1970s, he didn't become frustrated. At the time of his death in 2000, at age 82, he was working as a senior principal electrical engineer at Orbital Sciences in Chandler, AZ, helping design electrical systems on rockets. TR

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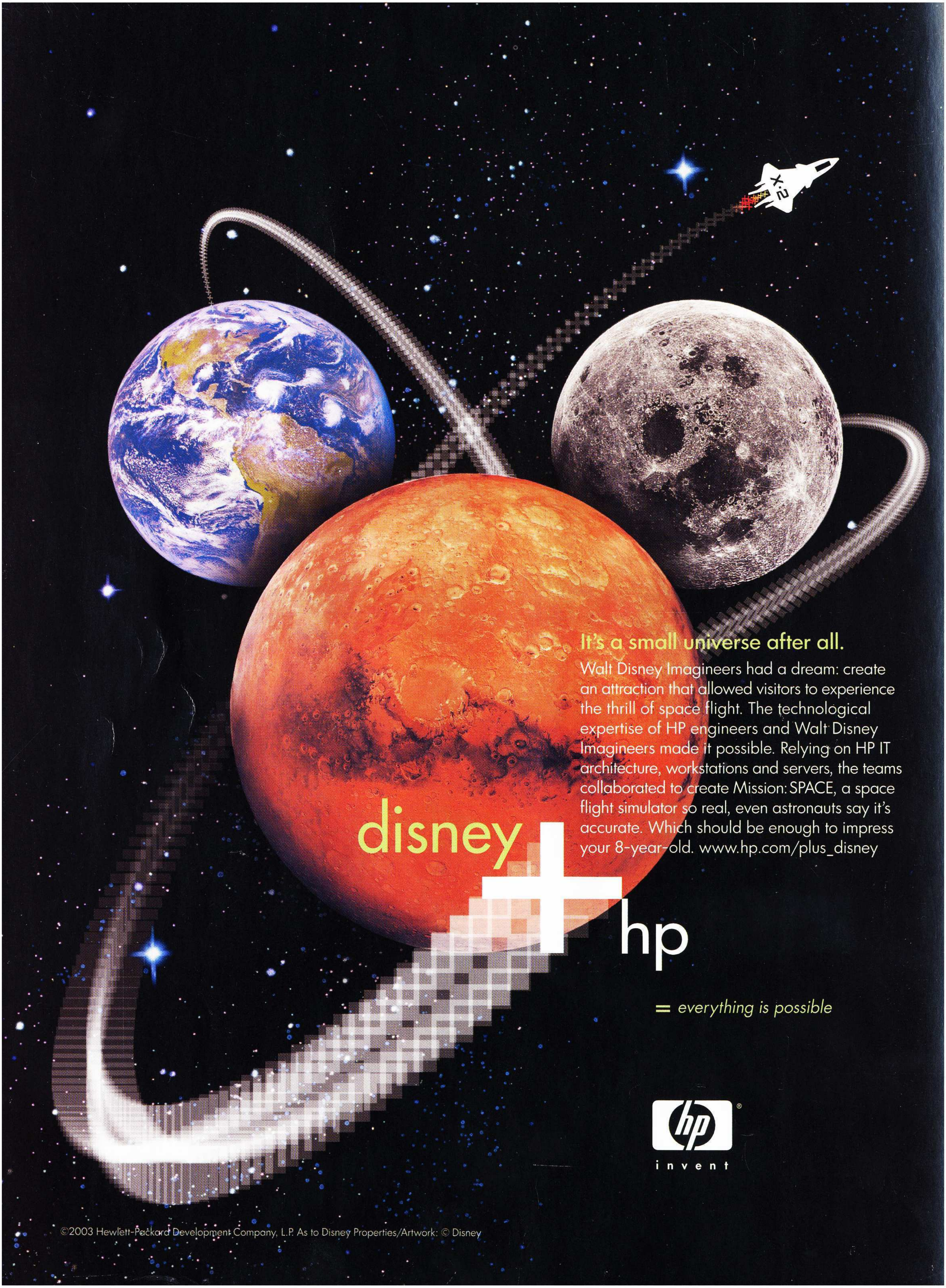
X-2
It's a small universe after all.
Walt Disney Imagineers had a dream: create an attraction that allowed visitors to experience the thrill of space flight. The technological expertise of HP engineers and Walt Disney Imagineers made it possible. Relying on HP IT architecture, workstations and servers, the teams collaborated to create Mission: SPACE, a space flight simulator so real, even astronauts say it's accurate. Which should be enough to impress your 8-year-old. www.hp.com/plus_disney
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